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STUDIES IN THE MECHANISM OF TRANSMISSION
OF NON-CONJUGATIVE SUBSTITUENT EFFECTS

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OF NON-CONJUGATIVE SUBSTITUENT EFFECTS

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SUMMARY

SECTION I

A series of 6-substituted spiro[3.3]heptane-2-carboxylic acids have been synthesized. The substituent groups are carboxyl, carbethoxy, cyano, bromo, amido, methyl and hydrogen. The pKa's of this series of acids were measured by potentiometric titration in 50 percent (weight) aqueous ethanol.

The pKa's were found to be well correlated by use of the empirical substituent parameter σ_I . Theoretical analysis of field effects by the Tanford modification of the Kirkwood-Westheimer equation using the spherical cavity model produced excellent agreement between calculated and experimental values for ΔpK_a . Independent assessments of effective dielectric through plots of pKa vs $\frac{\mu \cos \theta}{R^2}$ shows the Tanford modification to be quite adequate for this particular system.

Comparison of the spiro[3.3]heptyl system to the bicyclo[2.2.2]octyl and bicyclo[2.2.1]heptyl system points out the inadequacy of the σ -inductive effect for predicting relative abilities of hydrocarbon frameworks to transmit

substituent effects. At the same time comparison by the field effect model predicts very closely the experimental results.

SECTION II

Several series of bridge substituted bicyclo[2.2.2]-octane-2-carboxylic acids and ethyl esters have been synthesized where the substituents are either hydroxyl or epoxides. The pKa's of the acids have been determined by potentiometric titration and the rates of alkaline hydrolysis of the esters measured in 50 percent (weight) aqueous ethanol.

The σ -inductive effect predicts identical reactivities for the isomeric hydroxy acids. In contrast the pKa's are found to show a marked angular and distance dependence of substituent effect in substantial agreement with that predicted by the Tanford modification of the Kirkwood-Westheimer equation for field effects. The same results are found for the rates of alkaline hydrolysis of the esters. The order of reactivity for the four epoxide isomers is predicted exactly while the magnitude is within reasonable limits due to the limitations of the field theory.

CHAPTER I

INTRODUCTION

One of the problems of physical-organic chemistry which has received considerable attention for many years is the interpretation of the mechanism by which charged and dipolar substituents influence reactivity in remote reaction centers. Approaching these effects from basic electrostatic theory or through the use of empirical substituent parameters has met with limited success in explaining these mechanisms.

In a recent analysis Dewar and Grisdale (1) have recognized five distinct modes by which substituents may affect a distant reaction center.

- (1) The electric field set up by a polar or charged substituent may influence the reaction center through space (field effect).
- (2) The polarity of the substituent-substrate bond can be transmitted to the reaction center by successive polarization of the intervening σ bonds (σ -inductive effect).

- (3) The charge set up at a conjugated atom adjacent to the substituent may polarize the intervening π -electron system (π -inductive effect).
- (4) The π -electron system can be polarized by resonance interactions with the substituent (mesomeric effect).
- (5) There may be mutual conjugation between the substituent and reaction center through an intervening conjugated system (electromeric effect).

Clearly the above effects may be divided into two distinct categories -- non-conjugative and conjugative effects. Subsequent discussion will deal with the former, placing primary emphasis on field and σ -inductive effects and attempts to evaluate their relative importance in the transmission of substituent effects.

The Field Effect

Microscopic models for the effects of charged substituents on ionic equilibria, based on simplified treatments of the electrostatic situation, were initiated by Bjerrum (2) in his analysis of dissociation constants of

dicarboxylic acids. He equated the statistically corrected ΔpK of a diacid to the simple coulombic potential of one ionizable proton in the field of the other (Equation 1).

$$\log K_1/4K_2 = e^2/2.3 kTR_{ij}De, \quad (1)$$

where e = electrostatic charge

R_{ij} = distance between protons i and j

De = dielectric of material between protons

T = absolute temperature

k = Boltzmann's constant.

In this approach the dielectric constant was taken as that of the solvent. When experimental values of $\log K_1/4K_2$ were used to calculate R_{ij} , elongated straight chain acids gave reasonable results. With short chain acids, values of R_{ij} were much shorter than was expected on the basis of structural considerations.

Eucken (3) extended the Bjerrum approach to include dipolar substituents (Equation 2).

$$\log K_X/K_H = \frac{e\mu \cos \theta_{ij}}{2.3 kT R_{ij}^2 De}, \quad (2)$$

where e = electrostatic charge

μ = dipole moment of the substituent

θ_{ij} = angle between dipolar axis and R_{ij}

R_{ij} = distance from center of dipole to ionizable proton

T = absolute temperature

k = Boltzmann's constant

ϵ = dielectric constant of intervening medium.

However Eucken noted that the effective dielectric was intermediate between that of the solvent and the hydrocarbon portion of the acid. ϵ was discussed in terms of the fraction of lines of force passing through the solvent and the hydrocarbon portion. Experimental values of $\log K_X/K_H$ and assumed geometries were in fact used to calculate values for ϵ .

Smallwood (4), on the other hand, rationalized that since the molecular framework is a region of low dielectric, a value of unity should be used for the dielectric. This approach led to reasonable results when applied to acids containing dipolar substituents but not when applied to acids bearing charged substituents.

Kirkwood and Westheimer (5,6), recognizing that Eucken's arguments for an "effective dielectric" were of value, modified the earlier treatments by assuming that the

acid molecules were cavities of low dielectric ($D_i = 2$ because the framework is polarizable hydrocarbon material) embedded in a solvent continuum with its macroscopic dielectric constant.

A calculation of the electrostatic free energy for spherical and ellipsoidal cavities with arbitrary charge distribution immersed in a solvent of dielectric constant D_{ext} , leads to the expression $1/D_e = f_1/D_i + f_2/D_{\text{ext}}$ from which the "effective dielectric" D_e may be found. Similar expressions were developed for dipolar substituents. Tabulations of D_e for various cavity sizes, geometries, and solvent dielectrics have been presented by Westheimer, Jones and Lad (7).

Short chain fatty acids whose shapes roughly approximate spheres were used by Westheimer and Shookhoff (8) as a test of D_e calculated. The radii of the molecular cavities for diacids were found by using Traube's Rule (9). Using experimentally determined $\log K_1/4K_2$ values for these acids, a value for R was then determined. This value calculated fit between the values for maximum extension of the chain and the minimum value possible for free rotation. Similar treatment of dipolar substituted acids indicated that reasonable values for R could be obtained by using the ellipsoidal cavity model.

Since the actual geometric configuration of fatty acids in solution are extremely difficult to determine, only approximate solution of the question of field effects could be made. Clearly a rigid molecule of fixed geometry was essential to test the validity of the field effect.

Roberts and Moreland (10) prepared and examined the reactivities of a series of 4-substituted bicyclo[2.2.2]-octane-1-carboxylic acids and esters which they felt to be ideally suited for a quantitative test of the field effect since distances and angles could be estimated with considerable accuracy. Experimental $\log K_X/K_H$ values for acid ionization in 50 percent aqueous ethanol (volume) proved to be considerably higher than those predicted by the Kirkwood-Westheimer ellipsoidal cavity model. They concluded that the discrepancy between experiment and theory could be attributed to the following: (1) apparent rather than thermodynamic pK_a 's were determined, (2) calculated ΔpK_a 's are extremely sensitive to the values of R chosen and (3) residual inductive effects might be operative.

Such variation between theory and experiment led Tanford (11) to reexamine and modify the cavity model. He found that the depth at which a charge or dipole is imbedded within a molecular cavity is of considerably more importance

than is the size of the cavity. Adjusting the size of the cavity such that a charge was 1.0 \AA below the surface and a dipole 1.5 \AA led to considerably more accurate predictions of ΔpK_a 's than the Kirkwood-Westheimer approach, where the depth was simply a function of R and the size of the cavity as found by Traube's rules. Application of this refinement to the bicyclo[2.2.2]octane system gave calculated values for $\log K_X/K_H$ which more nearly approximated the observed values. He pointed out however that the appropriate depths might change from solvent to solvent.

Further work on rigid molecules of fixed geometry has been reported by Siegel and Kormarmy (12) who determined the pK_a 's of a series of trans-4-substituted cyclohexane-carboxylic acids in several solvents and found the Tanford modification of the Kirkwood-Westheimer equation (TMKW) to give results in fair agreement with experiment for ellipsoidal cavities.

Stock and Holtz (13) reexamined and extended the work of Roberts and Moreland on the bicyclo[2.2.2]octane system. A further refinement on the TMKW approach was introduced in that the values of D_e , R , and $\cos\theta$ for both the substituted and unsubstituted acids were used in the following way (Equation 3):

$$\log K_X/K_H = \frac{e}{2.3kT} \left[\left(\frac{\mu \cos \theta}{R^2 De} \right)_X - \left(\frac{\mu \cos \theta}{R^2 De} \right)_H \right] \quad (3)$$

Improvement in calculated $\log K_X/K_H$ values with respect to experiment was marked but significant variation remained. It was shown that values of $\log K_X/K_{NO_2}$ were predicted quite satisfactorily by TMKW for all groups but hydrogen and alkyl which implies that hydrogen and alkyl might be considered as abnormal. This is rationalized on the basis that the solvent continuum should begin closer to these lyophobic groups giving a higher value of De than predicted by the TMKW approach. In support of this argument a plot of $\mu \cos \theta / R^2$ versus pK_a reveals a linear relationship for all groups save hydrogen and alkyl, with a value for De of 5.6 predicted for this relationship.

Similar fair correlation between theory and experiment has been shown by Baker, Parish and Stock (14) for 4-substituted-bicyclo[2.2.2]oct-2-ene-1-carboxylic acids, 4-substituted-dibenzobicyclo[2.2.2]octa-2,5-diene-1-carboxylic acids and cubane-1,4-dicarboxylic acids as analyzed by the equation of Stock and Holtz. Calculated $\log K_X/K_H$ values for the dibenzo acids fit very well presumably because the benzene rings block the solvent continuum from approaching the lyophobic hydrogen substituent.

Calculated values of the octene acids could be correlated well with experiment by taking the chloro substituent as the standard rather than hydrogen for the reasons previously proposed.

Noyce, Bastian, Lau, Monson and Weinstein (15) have shown excellent agreement of kinetic data with rate constants calculated employing the TMKW model for the acetolysis of trans-4-substituted cyclohexyl methanesulfonates. Further Noyce and Johnston (16) have shown that the field effect model predicts quite well the reaction rates for the four stereoisomers of 4-substituted decalyl methanesulfonates.

Wilcox and Leung (17) have compared the ratios of $\log K_X/K_H$ for the 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids and the 4-substituted bicyclo[2.2.1]heptane-1-carboxylic acids and found the field effect model to be nearly perfect in predicting the relative efficiency of the two frameworks for the transmission of substituent effects. They stressed the cavity model was not sufficiently able to predict direct $\log K_X/K_H$ values.

Dewar and Grisdale (18) have proposed an alternate view of the field effect based on the following reasoning. The field of a dipolar bond is treated as being due to a point dipole located at the center of the bond with the

resulting potential varying as the inverse square of the distance. Since the dipole length is often comparable to the distance between reaction center and substituent, the situation becomes that of the interaction of two charges with the reaction center. Such interactions are functions of the inverse of the distance. Further, in solution the free end of the dipole may be solvated and have its charge dispersed over a shell of solvent molecules. On the other hand, the field due to the charge on the atom adjacent to the substituent will be propagated through the middle of the molecule. The net effect is that of a point charge at the point of attachment of the substituent, whose potential varies as the inverse power of the distance to the reaction center.

The meta-substituted benzoic acids were chosen as a standard of the field effect F , and the following expression developed (Equation 4),

$$F = (\sigma_x)_m r_{1,3} \quad (4)$$

where $(\sigma_x)_m$ is the meta substituent parameter based on the ionization of meta-substituted benzoic acids and $r_{1,3}$ the distance between the one and three carbon atoms of benzene.

σ_{ij} for any saturated system may be generated by dividing F by the distance between the carbon bearing the substituent and the carbon bearing the reaction center.

Using the field parameter and a parameter which measures combined π -inductive and mesomeric effects, Dewar and Grisdale generated σ values for various substituents on the biphenyl, naphthalene and terphenyl systems. These values, used in a Hammett-type equation showed good correlation between theory and experiment. Stock and Holtz (13) applied Dewar's field approach to the 4-substituted-bicyclo-[2.2.2]octane system with considerable deviation from linearity but postulated that the deviations were primarily due to resonance contributions to σ_m .

σ -Inductive Effect

An alternate treatment of substituent effects in saturated systems is the use of empirical relationships based on the idea of successive polarization of the sigma bonds between the substituent and the reaction center. The σ -inductive effect originated with Derick's (19) "Rule of Thirds" and is based on the observation that changes in the pK_a 's of acids can be correlated with the number of methylene groups interposed between the substituent and the carbonyl group of the acid.

Branch and Calvin (20) refined this approach and extended it to include substituent parameters. If one considers a substituent at position s in a molecule, the polarization of the substituent-substrate bond may produce an effect at the carbon to which the substituent is attached. This effect may be transmitted to another position in the molecule $s^{+}-n$, n bonds removed from the point at which the initial effect was exerted, by the successive polarization of the intervening σ bonds. The resulting effect at the reaction center, $\lambda_{s^{+}-n}$ will be equal to the initial effect λ_s , multiplied by a constant factor per bond ($1/f < 1$) and summed over all pathways (Equation 5).

$$\lambda_{s^{+}-n} = \lambda_s \sum_p (1/f)^{s^{+}-n} \quad (5)$$

The following empirical relationship proved to be quite reliable for the prediction of individual dissociation constants (Equation 6)

$$\log K_X = -4.75 + \frac{0.3 \sum I(1/f)^i}{1 + \left| \frac{0.03 \sum (1/f)^i}{\sum (1/f)^i} \right|} \quad (6)$$

where I is the inductive constant for a substituent group determined from substituted acetic acids. The fall-off factor f was set at 2.8 and i is the number of atoms between

substituent and the α -carbon of the carboxyl group. It may be pointed out that the value of I was constant in a particular solvent.

McGowan (21) has used a modified treatment of the σ -inductive effect according to the following equation (Equation 7):

$$-2.3 \text{ RT } \log K_X = -2.3 \text{ RT } \log K_H - BQ \quad (7)$$

where Q is the effective formal charge generated by a substituent, as determined from substituted acetic acids, and B the effect of a full formal charge at the carbonyl carbon (14 k-cal) times the sum of the $(1/f)^n$ values for each available pathway. McGowan was able to obtain fair correlation between theory and experiment by using a fall-off factor of 2 for the pK_a 's of substituted naphthylamines and the hydrolysis of *t*-cumyl chlorides. However when this approach was applied to the bicyclo[2.2.2]octanes considerable variation was noted.

Peterson and coworkers (22) conclude from their study of substituent effects in the addition of trifluoroacetic acid to terminally substituted 1-alkenes that the fall-off factor, f , for long chain aliphatics may be as low as 1.54. Stevenson and Williamson (23) have shown a fall-off factor

of 1.9 in studies on substituted alkyl amines.

Comparison of the Effects

Bowden (24) has attempted to compare the relative importance of field effects and σ -inductive effects through the use of a Hammett-type equation (Equation 8)

$$\log K_X/K_H = \sigma\rho \quad (8)$$

The substituent constant σ is considered to be independent of the nature of the reaction, and is a measure of the polar effect of a substituent relative to the unsubstituted compound. The reaction constant ρ for a reaction series is thus a measure of the susceptibility of a reaction to polar effects. Thus Bowden reasons that if the relative abilities of two systems to transmit substituent effects can be compared to their relative abilities as predicted by both the field and σ -inductive model, a distinction could be made between the two effects.

The 4-substituted-cyclohexane carboxylic acids and the para-substituted benzoic acids were chosen as the standards for the aliphatic and aromatic series respectively. Experimental ρ/ρ_0 values from a large number of different series were calculated where ρ_0 , the reaction constant for the standard, was set equal to one.

As a measure of field effect, Bowden used the Kirkwood-Westheimer model and assumed a constant effective dielectric in each solvent system. Thus $(\cos\theta/R^2)/(\cos\theta/R^2)_0$ could be taken as a measure of the relative abilities of the molecules to transmit substituent effects when compared to the ρ/ρ_0 values experimentally obtained.

The approach of Branch and Calvin was used as a measure of the inductive effect. Bowden assigned fall-off factors of 2.08 for sp^3 carbon, 1.49 for sp^2 carbon and 1.67 for sp carbon. Using the appropriate fall of factors and the same standard systems as in the field effect, comparisons could be made between the relative abilities of two frameworks to transmit substituent effects by the inductive mode.

Systems involving conjugation gave excellent agreement between the field effect and experiment. However the non-conjugative systems showed fair correlation for both theoretical models. The conclusion drawn by Bowden was that substituent effects are best understood in terms of both inductive and field models.

A second method to compare the relative importance of the two limiting models (field and σ -inductive) is to devise sets of model compounds in which one of the effects

is held constant while the other is allowed to vary. Baker, Parish and Stock (14) have determined the dissociation constants of 1,4-bicyclo[2.2.2]octane dicarboxylic acid and 1,4-cubane dicarboxylic acid. The field effect predicts nearly identical values for $\log K_1/4K_2$ in the two systems. However the cubane acid has six pathways for the inductive effect and the octane only three. The experimental results in this case indicate that the substituent effect is independent of the number of pathways available for its transmission.

Wilcox and Leung (17) recognized that the quality of fit between predictions of the field model and experiment has not been sufficiently good to justify a semi-empirical distinction between the field and inductive models. They devised an approach to transfer the burden of distinction from the difficult-to-analyze field effect model to the simple inductive model. The inductive model predicts a ρ/ρ ratio of from 1.33-1.67 for the relative ability to transmit effects in the 4-substituted bicyclo[2.2.1]heptane-1-carboxylic acids as compared to the 4-substituted-bicyclo[2.2.2]octane-1-carboxylic acids as the fall-off factors are varied from 2.0 to 3.0. The field effect predicts ρ/ρ ratios of 1.20. The ρ/ρ ratios found in several solvent systems

fall within two percent of the values predicted by the field model. It is concluded the inductive component of the total substituent effect must be minor.

Further evidence for a field effect may be found by holding the number of bonds between the reaction center and substituent constant and varying the angle and distance of the substituent. Stock and Golden (25) have claimed reversal of normal substituent effects in 8-substituted-9,10-ethanoanthracene-1-carboxylic acids. That is, a substituent which normally causes the acid to be stronger than the unsubstituted acid causes the acid to be weaker when the substituent is held in an atypical configuration. The inductive effect predicts a strengthening of the acid with respect to the unsubstituted case.

Similar reversal of substituent effects were noted by Bowden and Parkin (26) in 8-substituted-1-naphthoic acids. Complimentary observations of an angular dependence of substituent effects in substituted naphthoic acids and fluoro-naphthalenes were reported by Dewar and Grisdale (18), Wells and Adcock (27), and Adcock and Dewar (28). Grubbs and Fitzgerald (29) have observed angular dependence of substituent effects in geometrical isomers of 11,12-dichloro-9,10-ethanoanthracene-2-carboxylic acids and esters. However

reversal of substituent effect was not seen in this case as might have been expected, nor were these cases successfully correlated with the Kirkwood-Westheimer cavity model.

In view of the arguments presented for the field and σ -inductive effects it is clear that more information is needed on desirable model compounds. In the past, most investigations of substituent effects have centered on aromatic systems with relatively little data on saturated systems of fixed geometries. Ehrenson (30) in his review of structure-reactivity relationships concludes that "both inductive and direct field interactions as currently pictured are likely contributing factors in substituent effects upon reactivity."

In order to compare the various empirical and theoretical approaches to substituent effects and to extend the analysis of the two limiting models (field and σ -inductive) for their propagation, we have chosen two new saturated model systems. Section I of this thesis is concerned with the preparation and examination of the dissociation constants of 6-substituted spiro[3.3]heptane-2-carboxylic acids and Section II with the preparation of several bridge substituted bicyclo[2.2.2]octane-2-carboxylic acids and esters and the determination of their reactivities.

CHAPTER II

INSTRUMENTATION, EQUIPMENT AND SOLVENTS

Instruments and Equipment

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded with Perkin-Elmer Infracord and Perkin-Elmer 457 spectrophotometers with solids in the form of potassium bromide pellets and liquids as thin films on sodium chloride plates. Nuclear magnetic resonance (nmr) spectra were recorded with a Varian A-60 spectrometer using the solvent specified. Chemical shifts are reported in τ referenced to tetramethylsilane. The abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet, respectively and are suffixed by the number of protons.

Gas-liquid chromatography (glc) was performed using an F and M Gas Chromatograph, Model 700, with thermal conductivity detectors. Columns were six feet by one-eighth inch stainless steel with packings of ten percent SE-30 on firebrick, five percent carbowax 20-M on Chromsorb W and 15 percent 1,2,3-tris(2-cyanoethoxy)propane on 60/70 Gas Chrom P. Mass spectra were recorded using a Varian M-66

mass spectrometer. Measurements of pH were made using a Beckman Research pH meter, Model 1019. Column chromatography was performed in glass columns using silica gel. Constant temperature baths were controlled by a Sargent Thermonitor. Carbon, hydrogen and nitrogen analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Linear least squares analyses were carried out on the Burroughs 5500 at the Rich Computer Center with a least squares curve-fitting equation written by E. L. Eichhorn (Burroughs Professional Services).

Purification of Solvents

Benzene

Stock benzene was washed with concentrated sulfuric acid, dried over calcium chloride and distilled.

Chloroform

Stock chloroform was washed with concentrated sulfuric acid, dried over calcium chloride and distilled.

Ethanol

Stock 100 percent ethanol was refluxed with magnesium and distilled.

Ether

Fisher Anhydrous Ether was used without further purification.

Methanol

Stock methanol was refluxed with magnesium and distilled.

Tetrahydrofuran

Fisher reagent grade was dried over lithium aluminum hydride and distilled.

Water

Distilled water was redistilled from alkaline potassium permanganate with protection from carbon dioxide by an Ascarite tube.

CHAPTER III

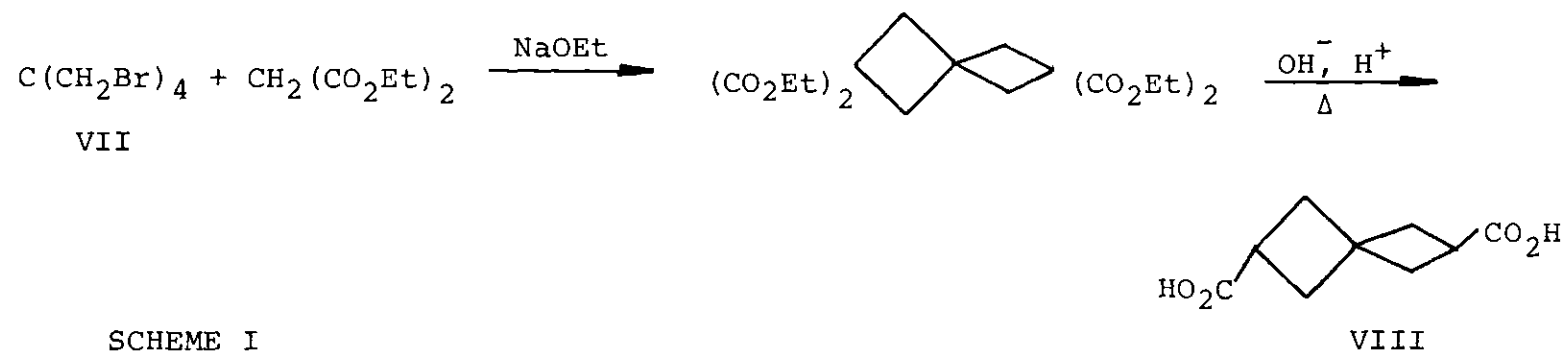
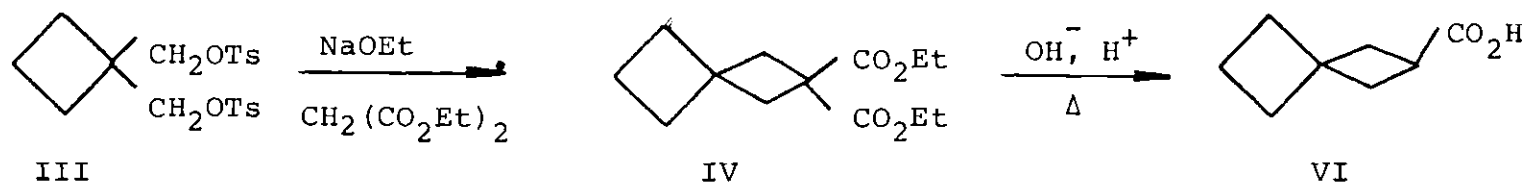
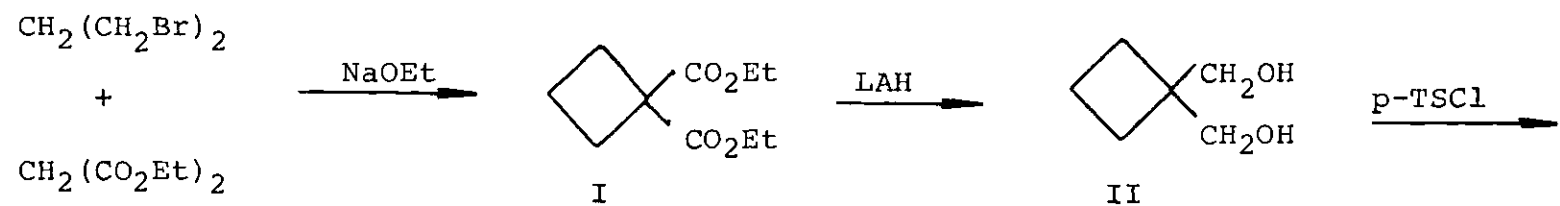
EXPERIMENTAL - SECTION I

Preparation of 6-Substituted Spiro-
[3.3]heptane-2-carboxylic Acids

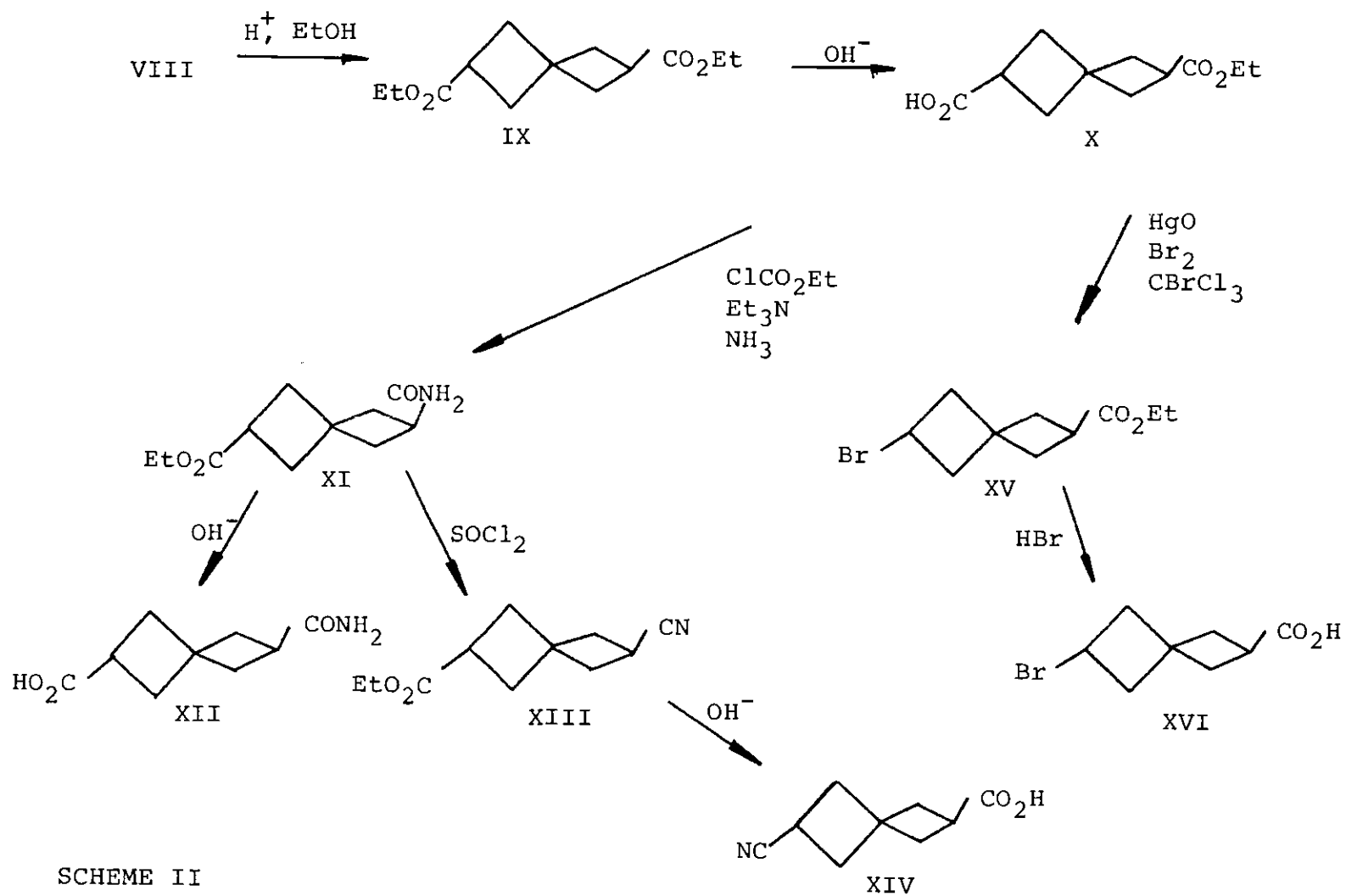
The general outline for the preparation of 6-substituted spiro[3.3]heptanes is presented in schemes I and II.

Diethyl Cyclobutane 1,1-Dicarboxylate (I)

Following a previously described procedure (31), sodium ethoxide was prepared in a one liter flask, fitted with a reflux condensor and calcium chloride drying tube by adding 23.1 g (1.0 mole) of freshly cut sodium to 500 ml of absolute ethanol. A three-necked, round bottom flask, fitted with a reflux condensor and two dropping funnels, was charged with 300 ml of sodium ethoxide solution and 95.0 g (0.51 mole) of diethyl malonate. While the mixture refluxed, 99.2 g (0.49 mole) of 1,3-dibromopropane and 200 ml of sodium ethoxide were added simultaneously from the dropping funnels over a one hour period. Refluxing was continued for 90 minutes after which about 400 ml of ethanol were distilled from the mixture. The cooled residue was



SCHEME I



dissolved in 300 ml of water and extracted with two-300 ml portions of benzene. The combined benzene layers were dried over magnesium sulfate and the benzene removed in vacuo. The remaining liquid was distilled on a spinning band column. The fraction of b.p.₁₂ 110°C (lit. b.p.₁₅ 105-112°C) (31) contained 46.6 g (46.2 percent) of I; $\nu_{\text{max}}^{\text{neat}}$ 2950, 1700, 1450, 1420, 1350 cm^{-1} .

1,1-Bis-hydroxymethyl Cyclobutane (II) (32)

To a stirred suspension of 11.0 g (0.29 mole) of lithium aluminum hydride in 375 ml of anhydrous diethyl ether was added dropwise 46.6 g (0.23 mole) of I in 115 ml of anhydrous ether. Stirring was continued two hours after which the suspension was cooled in an ice bath and 19 ml of water cautiously added dropwise. The resulting sludge was filtered and dissolved in 150 ml of 20 percent (volume) sulfuric acid. The pH of the solution was adjusted to 3.0 by the addition of sodium carbonate. The solution was extracted with ether overnight on a continuous extraction apparatus. The ether was dried over magnesium sulfate and evaporated in vacuo. The liquid residue was distilled on a spinning band column yielding 18.8 g II (65 percent) b.p._{0.4} 82-83°C (lit. b.p.₃ 112-115°C) (32); $\nu_{\text{max}}^{\text{neat}}$ 3330, 2900, 1450, 1030 cm^{-1} .

1,1-Bis-hydroxymethyl Cyclobutane Ditosylate (III) (33)

To 135 ml of dry pyridine, cooled to 0°C, was added 18.8 g (0.15 mole) of II. Paratoluenesulfonyl chloride, 68.0 g (0.35 mole), was added in small portions over a two hour period. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The mixture was poured into 200 ml of concentrated hydrochloric acid which contained 200 g of crushed ice. The resulting precipitate was filtered and washed successively with ice cold 1.0 N hydrochloric acid and ice water. The tan solid was recrystallized from methanol to give 49.7 g (75 percent) III of m.p. 91-93°C (lit. 95°C) (33).

Diethyl Spiro[3.3]heptane-2,2-dicarboxylate (IV) (33)

To 280 ml of dry xylene was added 74.2 g (0.46 mole) diethyl malonate and 6.2 g (0.27 mole) of cut sodium. The mixture was heated until all the sodium had reacted. Then 49.7 g (0.11 mole) of compound III was added and the mixture refluxed 12 hours. The mixture was allowed to cool and 250 ml of water was added. The xylene layer was removed and the water layer was extracted with two-250 ml portions of xylene. The xylene layers were combined, dried over magnesium sulfate and the xylene removed in vacuo. The residue was distilled on a spinning band column yielding 19.2 g

(71 percent) compound IV; b.p._{0.1} 80-81°C (lit. b.p._{0.2} 87°C) (33).

Spiro[3.3]heptane-2,2-dicarboxylic Acid (V)

Hydrolysis of 9.6 g (0.04 mole) of IV was accomplished by refluxing with 10.0 g of potassium hydroxide in 80 ml of absolute ethanol for 45 minutes. The precipitate from the cooled reaction mixture was filtered from the ethanol and dissolved in a minimum of water. Cold 50 percent (volume) sulfuric acid was added dropwise until a pH of 1.0 was reached. The resulting white crystals were filtered and washed with a small portion of ice water and dried in vacuo yielding 4.6 g V (62 percent); m.p. 199°C decarboxylates (lit. m.p. 200°C decarboxylates) (33); $\nu_{\text{max}}^{\text{KBr}}$ 3000, 2700, 1730, 1400, 1290 cm^{-1} .

Spiro[3.3]heptane-2-carboxylic Acid (VI)

Decarboxylation of 1.9 g (0.01 mole) of V was accomplished by heating at 210°C in an oil bath for 30 minutes. The black residue was dissolved in dry ether and filtered. The ether was evaporated in vacuo and the liquid residue distilled on a small spinning band column. The fraction b.p._{2.0} 105-107°C (lit. b.p.₁₂ 126-127°C) (33) yielded 1.0 g (70 percent) compound VI; neutralization equivalent: calcd. 140.18, found 141.28; $\nu_{\text{max}}^{\text{neat}}$ 3000, 2700, 1680, 1400,

1320 cm^{-1} ; nmr (DCCl_3) τ : -2.00 (s,1), 7.10 (m,1), 7.91 (m,10).

Pentaerythrityl Tetrabromide (VII) (34)

A three-necked, three liter flask fitted with a powerful mechanical stirrer, thermometer, and dropping funnel was charged with 98 g (0.71 mole) pentaerythritol and 500 ml of dry pyridine. The flask was cooled in an ice bath and 565 g (3.19 moles) of benzenesulfonyl chloride was added over a period of two hours with care being taken that the temperature did not rise above 35°C . The reaction mixture was stirred one hour and then added slowly to 600 ml of concentrated hydrochloric acid in 750 ml of water and two liters of methanol. The suspension was cooled by adding 500 grams of ice, filtered and washed with five liters of cold water and one liter of cold methanol. The solid was air dried and powdered. This was then added to one liter of diethylene glycol in a three liter, three-necked flask fitted with a mechanical stirrer. The mixture was heated in an oil bath to $160\text{--}170^\circ\text{C}$ while 600 g (5.80 moles) of sodium bromide was added. The mixture was heated for 12 hours. After the reaction was cooled, two liters of ice water were added. The resulting white precipitate was filtered, washed with cold water, and air dried. The solid was

recrystallized from acetone, yielding 188.3 g (68.4 percent) of VII of m.p. 156-157.5°C (lit. 156.5-158°C) (34).

Spiro[3.3]heptane-2,6-dicarboxylic Acid (VIII) (35)

A five liter round bottom flask, fitted with a reflux condensor and calcium chloride drying tube, was charged with 2.5 liters of amyl alcohol and 57.5 g (2.5 moles) of sodium. When dissolution was complete, 400 g (2.5 moles) of diethyl malonate was added followed by 188.3 g (0.49 moles) of VII. The mixture was heated and distilled until the vapor temperature reached 130°C to remove the ethanol formed by ester exchange. Amyl alcohol equal to the volume of the distillate was added and the mixture refluxed three days.

Most of the amyl alcohol was removed by distillation and water added so the remainder would be removed as the azeotrope. The layer which formed over the water was removed and the water extracted with ether. These layers were combined and the ether was evaporated in vacuo. The residue was saponified in 3.75 liters of ethanol with 450 g (7.5 moles) of potassium hydroxide at room temperature for 48 hours. The resulting salt was filtered, dissolved in water, treated with decolorizing charcoal and acidified with concentrated hydrochloric acid. The mixture was then extracted with ether for a 48 hour period.

The ether extract was dried over magnesium sulfate and removed in vacuo. The solid residue was heated to 200°C in an oil bath, until gas evolution ceased. The brown mass remaining was dissolved in one liter of boiling water and decolorized with charcoal. Diacid VIII, 24.6 g (27 percent), was recovered by concentration of water in vacuo. Recrystallization from ethyl acetate gave white crystals, m.p. 210-211.5°C (lit. 212°C) (35); neutralization equivalent: calcd. 92.10, found 92.50; $\nu_{\text{max}}^{\text{KBr}}$ 3000, 1700, 1420, 1320, 1250 cm^{-1} .

Diethyl Spiro[3.3]heptane-2,6-dicarboxylate (IX)

Diacid VIII, 24.6 g (0.13 mole), was dissolved in 600 ml of absolute ethanol and 6.2 ml of concentrated sulfuric acid. After 24 hours of refluxing, the reaction mixture was poured into an equal volume of cold ten percent sodium bicarbonate solution. The solution was extracted several times with chloroform. The chloroform was dried over magnesium sulfate and evaporated in vacuo. Diester IX, 28.0 g (87 percent), was obtained by distillation, b.p._{1.5} 95-96°C; $\nu_{\text{max}}^{\text{neat}}$ 2960, 1725, 1460, 1430, 1030 cm^{-1} ; nmr (DCCl_3) τ : 5.90 (q,4), 7.10 (m,2), 7.75 (m,8), 8.76 (t,6).

6-Carbethoxyspiro[3.3]heptane-2-carboxylic Acid (X)

Following a previously described procedure (36) for

converting diester to half-ester, 49.9 g (0.21 mole) IX was refluxed 26 hours with 7.72 g (0.138 mole) of potassium hydroxide in 200 ml of absolute ethanol. The reaction mixture was poured into 500 ml of ice water and extracted with ether in three-200 ml portions to remove unreacted starting material. The water layer was acidified with hydrochloric acid to a pH of about two and extracted with ether in three-200 ml portions. The extract was dried over magnesium sulfate and the ether removed in vacuo. The residue was distilled yielding 17.5 g (39 percent) half-ester X; b.p.₃ 157-165°C and solid VIII. Neutralization equivalent: calcd. 212.25, found 212.63; Anal. calcd. for $C_{11}H_{16}O_4$: C, 62.24; H, 7.61. Found: C, 62.03; H, 7.93; ν_{\max}^{neat} 3000, 2900, 2650, 2560, 1730, 1700 cm^{-1} ; nmr (DCCl_3) τ : -1.50 (s,1), 5.85 (q,2), 6.95 (m,2), 7.72 (m,8), 8.80 (t,3).

Ethyl 6-Amidospiro[3.3]heptane-2-carboxylate (XI)

By analogy to previously reported procedures (36), 3.17 g (0.015 mole) of half-ester X and 1.5 g (0.015 mole) were added to 70 ml of dry chloroform and cooled in an ice bath. Then 1.59 g (0.015 mole) of ethyl chloroformate was added and the solution stirred 15 minutes. Anhydrous ammonia was bubbled through the solution and the resulting suspension stirred overnight. The ammonium chloride was

filtered off and washed with chloroform. The chloroform was removed in vacuo and the tan residue recrystallized from hot benzene-petroleum ether to give 1.57 g (49.5 percent) of flaky white XI, m.p. 132-133°C. Anal. calcd. for $C_{11}H_{17}NO_3$: C, 62.5; H, 8.06; N, 8.06. Found: C, 62.7; H, 8.18; N, 7.76. ν_{\max}^{KBr} 3330, 3100, 2900, 1720, 1645, 1610 cm^{-1} ; nmr ($DCCl_3$) τ : 5.84 (q,2), 7.00 (m,2), 7.78 (m,8), 8.73 (t,3).

6-Amidospiro[3.3]heptane-2-carboxylic Acid (XII)

Saponification of 0.998 g (0.0042 mole) of amide-ester XI was carried out in 11.9 ml of 0.46 N alcoholic potassium hydroxide at room temperature overnight. Thirty ml of water were added and the solution extracted with three-40 ml portions of ether to remove starting material. The aqueous layer was acidified with 6 N hydrochloric acid to a pH of two and extracted with ether overnight. The extract was dried over anhydrous magnesium sulfate followed by evaporation of the ether in vacuo. The residue was recrystallized from acetone to give a white powder, 0.187 g of XII (24.6 percent) m.p. 178-179°C. Anal. calcd. for $C_9H_{13}NO_3$: C, 59.0; H, 7.10; N, 7.65. Found: C, 58.9; H, 6.84; N, 7.20; ν_{\max}^{KBr} 3380, 3200, 2740, 2540, 1695, 1650, 1585 cm^{-1} ; neutralization equivalent: calcd. 183.21, found 184.56.

Ethyl 6-Cyanospiro[3.3]heptane-2-carboxylate (XIII) (37)

Dehydration of the amide ester was carried out by refluxing 4.03 g (0.019 mole) XI in 90 ml of thionyl chloride for one hour. Excess thionyl chloride was removed in vacuo leaving a yellow liquid in which a small amount of solid was suspended. The mixture was centrifuged and the supernatant liquid distilled to yield 2.93 g (80 percent) of pure cyano ester, b.p._{2.5} 110°C; $\nu_{\text{max}}^{\text{neat}}$ 2970, 2260, 1730 cm^{-1} ; nmr (DCCl_3) τ : 6.05 (q,2), 7.10 (m,2), 7.80 (m,8), 8.85 (t,3).

6-Cyanospiro[3.3]heptane-2-carboxylic Acid (XIV)

Saponification of 2.90 g (0.015 mole) of XIII was accomplished by refluxing three hours with 0.83 g (0.015 mole) potassium hydroxide in 25 ml of 95 percent ethanol. Fifty ml of water were added and the solution extracted three times with equal volumes of ether to remove starting material. The water layer was acidified with 6 N hydrochloric acid to a pH of two and extracted with three portions of ether. The extract was dried over magnesium sulfate followed by evaporation of the ether in vacuo. The residue was recrystallized from ether-n-hexane to give 1.07 g (43.3 percent) of white crystalline XIV. This was sublimed at 40°C and two mm, m.p. 100-101°C. Neutralization equivalent: calcd. 165.20, found 167.33. Anal. calcd. for

$C_9H_{11}NO_2$: C, 65.43; H, 6.72; N, 8.48. Found: C, 65.37; H, 6.76; N, 8.37; ν_{\max}^{KBr} 2740, 2640, 2210, 1685 cm^{-1} ; nmr (DCCl₃) τ : -1.17 (s,1), 7.00 (m,2), 7.55 (m,8).

Ethyl-6-bromospiro[3.3]heptane-2-carboxylate (XV)*

Mercuric oxide (red) (8.84 g, 0.04 mole) was added to 12.05 g (0.057 mole) of half-ester X dissolved in 180 ml of bromotrichloromethane. The mixture was heated to 70-80°C with stirring and 8.86 g (0.054 mole) of bromine dissolved in 72 ml of bromotrichloromethane added from a dropping funnel. Upon completion of addition, the reaction was heated for one hour. A white salt precipitated on cooling to room temperature and was filtered off. The filtrate was washed with ten percent sodium bicarbonate to remove unreacted acid. Residual bromine was extracted with sodium bisulfite solution. The organic layer was dried over Drierite and the solvent removed in vacuo. Attempts at distillation resulted in pyrolysis. The bromo ester XV was obtained in 39 percent yield by silica gel column chromatography using benzene as a solvent; ν_{\max}^{neat} 2950, 1730, 1430, 1370, 1340 cm^{-1} ; nmr (neat) τ : 5.90 (q,2), 7.45 (broad m, 9), 8.85 (t,3).

* prepared by G. H. Greene and R. L. Joyner.

6-Bromospiro[3.3]heptane-2-carboxylic Acid (XVI)*

Bromo ester XV (0.92 g, 0.0037 mole) was added to 20 ml of 48 percent hydrobromic acid and stirred for ten hours at room temperature. The mixture was diluted with 25 ml of ice water and extracted with three-20 ml portions of chloroform. The chloroform extract was washed with three-20 ml portions of cold water and dried over magnesium sulfate. The chloroform was removed in vacuo leaving light tan crystals which were recrystallized from benzene-petroleum ether yielding 0.35 g (43 percent) bromo acid XVI, m.p. 122-123°C; neutralization equivalent: calcd. 219.09, found 222.59.

Determination of the pKa's of the

6-Substituted Spiro[3.3]heptane-2-carboxylic Acids

The pKa's of the various 6-substituted spiroheptanes were determined by potentiometric titration in 50 percent (weight) aqueous ethanol (25,38,39,40) using a Beckman model 1019 pH meter with glass and calomel electrodes.

Solvent and Solutions

The solvent was prepared by mixing equal weights of freshly purified water and absolute ethanol. The solvent

*prepared by G. H. Greene and R. L. Joyner.

was stored in sealed brown bottles under an atmosphere of nitrogen.

Standard sodium hydroxide solution was prepared by diluting 1.5 ml of 6.66 N sodium hydroxide to one liter with 50 percent aqueous ethanol. The solution was standardized by titration with potassium acid phthalate and found to be $1.021 \times 10^{-2}N$. This was stored at 25°C in sealed polyethylene bottles under an atmosphere of nitrogen.

Buffer solution for calibration of the pH meter was prepared by dissolving 0.0907 g of freshly sublimed benzoic acid in 100 ml of aqueous ethanol. The molarity of the acid was found to be $7.40 \times 10^{-3}M$ by titration with the standard base. Benzoic acid-sodium benzoate buffer was then made by adding exactly one-half the volume of standard base required to neutralize 40 ml of the benzoic acid solution (39,10). The buffer was stored in a capped bottle under a blanket of nitrogen.

Freshly recrystallized, distilled or sublimed spiro acids were weighed into clean, dry 50 ml volumetric flasks and were made up to the mark with solvent which had been stored at 25°C. In each case these solutions were made up to be as close to $7.4 \times 10^{-3}M$ as possible. The capped flasks were then stored in the constant temperature bath at 25°C until they were titrated.

Apparatus and Titrations

The pH measurements were made in a 100 ml tall form beaker which was clamped in the constant temperature bath. The beaker was fitted with a rubber stopper through which were inserted the electrodes, a nitrogen inlet tube, a NBS thermometer and the tip of the base dispensing burette. Stirring was accomplished by means of a Teflon encased stirring bar propelled by an air driven magnetic stirrer. Solvent saturated nitrogen was slowly admitted to the beaker throughout the measurements.

The pH meter was calibrated with the benzoic acid buffer to read 5.738, which is the reported thermodynamic pKa of benzoic acid in 50 percent (weight) aqueous ethanol (13,41). The meter was checked with buffer between each set of measurements to insure against drift. Significantly no adjustment was necessary throughout the measurements which took several hours.

Forty milliliters of the acid solution to be titrated was introduced to the beaker by volumetric pipette. The solution was stirred as standard base was added rapidly from the burette. The addition of base was stopped when enough had been added to come within one ml of the anticipated half-neutralization point of the acid. Stirring was

continued until the temperature within the beaker had re-established itself at 25°C. Stirring was then discontinued and the pH of the solution and the volume of base added recorded. This procedure was then repeated with base being added in increments between 0.1 and 0.2 ml until a point one ml beyond the anticipated half-neutralization point was reached.

The equivalence point of the acid solutions were confirmed by titration. Base was added rapidly to a point about one ml short of the anticipated equivalence point. The pH and volume of base were recorded in increments of about 0.1 ml. The equivalence point was taken as the point where the slope of a pH vs volume plot is greatest. This may be calculated from $\Delta\text{pH}/\Delta \text{ml}$ data and the equivalence point is that point at which this value is a maximum.

Treatment of Data

The data from about the half-neutralization point are used to calculate the pKa of the acid by the Henderson-Hasselbach equation (42), (Equation 9).

$$\text{pKa} = \text{pH} + \log \frac{[\text{acid}]}{[\text{salt}]} \quad (9)$$

This formulation is easily derived from the expression for dissociation constant of the acid, (Equation 10).

$$K_a = \frac{[H^+][A^-]}{[HA]} \quad (10)$$

Once the initial concentration of acid is confirmed from the equivalence point the concentration of residual acid and salt may be found from the volume of base added at that point. The pH recorded for each data point is then used to calculate the pKa of the acid at that point. The pKa's thus found are then averaged to give a pKa for the acid from that particular measurement. Table 1 shows the method of calculation for the hydrogen substituted spiro[3.3]-heptane-2-carboxylic acid. Deviations of pKa for a single point were never more than 0.003 from the average while the average deviation in a single run was usually less than ± 0.001 .

The pKa's from the measurements of three independently prepared solutions were averaged to give the pKa for each spiro acid and the average deviation.

Corrections for liquid junction potentials and activity coefficients were made empirically by assuming that the carboxylate anions had the same intrinsic mobility and activity as the reference benzoate anion (17,43,44,45,50). This assumption appears to be justified since the measurements were made at the same ionic strength as the reference buffer (0.0025 ± 0.0001).

Table 1. The Calculation of the pKa of Spiro[3.3]heptane-2-carboxylic Acid by the Henderson-Hasselbach Equation

ml base	moles salt X 10 ⁵	moles acid X 10 ⁵	ratio $\frac{HA}{A^-}$	log $\frac{HA}{A^-}$	pH	pKa
0.0	0.0	2.4837	--	--	--	--
11.74	1.1975	1.2862	1.0741	0.031	6.231	6.262
11.84	1.2077	1.2760	1.0566	0.024	6.240	6.264
12.00	1.2240	1.2597	1.0292	0.012	6.250	6.262
12.10	1.2342	1.2495	1.0124	0.005	6.258	6.263
12.24	1.2485	1.2352	0.9894	-0.005	6.266	6.261
12.34	1.2587	1.2250	0.9733	-0.012	6.275	6.263
12.46	1.2709	1.2128	0.9543	-0.020	6.283	6.263
12.56	1.2811	1.2026	0.9387	-0.027	6.290	6.263
24.35	2.4837	0.0	--	--	--	--
Average pKa 6.263 ± 0.001						

Special treatment was required for the diacid since there are two ionizable protons to be considered (Equations 11 and 12).

$$K_1 = \frac{[H^+][HA^-]}{[H_2A]} \quad (11)$$

$$K_2 = \frac{[H^+][A^-]}{[HA^-]} \quad (12)$$

The individual dissociation constants may be derived by an iterative procedure using data collected at the one-quarter and three-quarter neutralization points by the use of Equations 13 and 14 (38,46),

$$K_1 = [H^+]_{1/4} \frac{[H^+]_{1/4}}{3K_2 + [H^+]_{(1/4)}} \quad (13)$$

$$K_2 = [H^+]_{3/4} \frac{3[H^+]_{3/4} + K_1}{K_1} \quad (14)$$

where $[H^+]_{1/4}$ and $[H^+]_{3/4}$ are the hydrogen ion concentrations at the one-quarter and three-quarter neutralization points respectively. For the calculation K_2 is assumed to be equal to $[H^+]_{3/4}$ and K_1 is found according to equation 13. The value of K_1 calculated is then used in equation 14 to find a better value for K_2 . The newly calculated value of K_2 is inserted in equation 13 and the procedure continued

until both K_1 and K_2 remain constant.

The values of K_1 and K_2 must be statistically corrected (5). K_1 is divided by two since there are two acid functions per molecule. K_2 is correspondingly multiplied by two since there are twice as many carboxylate groups to which the proton may return.

CHAPTER IV

DISCUSSION OF RESULTS - SECTION I

The pKa values of a series of 6-substituted spiro-[3.3]heptane-2-carboxylic acids as determined in 50 percent (weight) aqueous ethanol are summarized in Table 2. These results will be compared to the various empirical and theoretical approaches to substituent effects.

Empirical Correlations

Polar effects of substituents on the acidities of the bicyclo[2.2.2]octane, bicyclo[2.2.2]octene and dibenzobicyclo[2.2.2]octadiene systems have been shown by Stock and his students to be well correlated by σ_I (13,14). Taft and his associates have shown the many applications of the polar substituent constant, σ_I , in aliphatic reactivities (47,48). The use of these parameters to describe the relative pKa's of the spiro acids is shown in Figure 1. σ_I parameters based on chemical reactivities of substituted acetic acids were taken from Charton's extensive compilations (49). The correlation equation is given as follows:

$$\text{pKa} = -0.693 \sigma_I + 6.288$$

Table 2. pKa's of 6-Substituted Spiro[3.3]heptane-2-carboxylic Acids, 25°C

Substituent	pKa
H	6.266 ± 0.015
CN	5.856 ± 0.018
Br	5.980 ± 0.015
CO ₂ C ₂ H ₅	6.062 ± 0.025
CH ₃ [*]	6.321 ± 0.015
CO ₂ H ^a	6.096 ± 0.010
CO ₂ ^{-a}	6.450 ± 0.015
CONH ₂	6.110 ^b

*Prepared and measured by R. L. Joyner, private communication

^aStatistically corrected

^bOne measurement

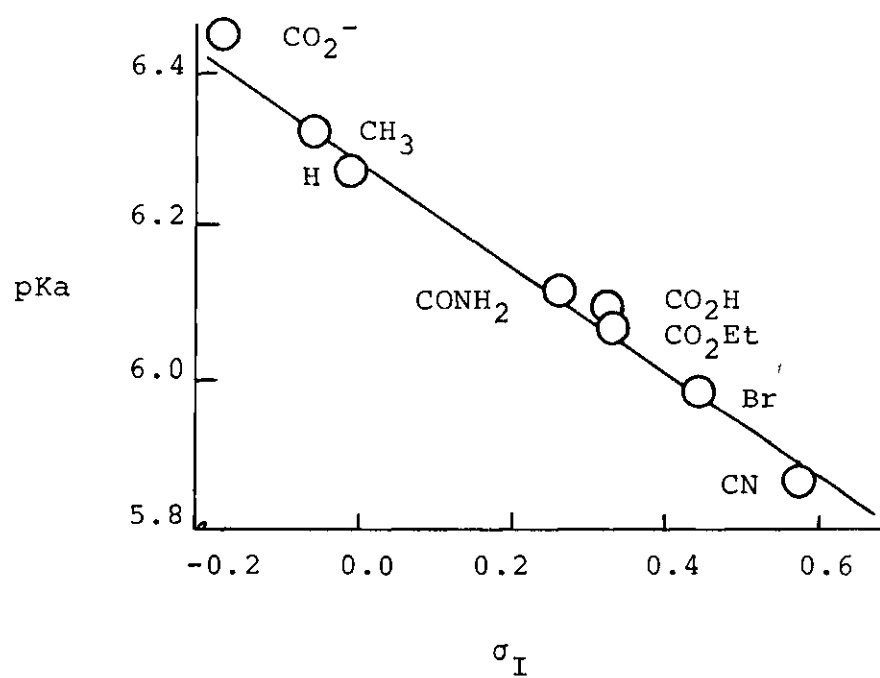


Figure 1. Correlation of pKa with σ_I

The high degree of correlation ($r = 0.995$, $s = 0.205$, $n = 8$) (50) provides additional evidence that σ_I is a good measure of non-conjugative substituent effects.

Application of the Dewar-Grisdale (18) approach to the spiro acids, as shown in Figure 2, produces a fair correlation ($r = 0.941$, $s = 0.550$, $n = 7$). $\sigma_{2,6}$ parameters

$$\text{pKa} = -1.33 \sigma_{2,6} + 6.300$$

were generated from F parameters of m-substituted benzoic acids where $\sigma_{2,6} = F/R_{2,6}$, $F = 1.73 \sigma_m$ and $R_{2,6}$ is the distance from carbon two to carbon six in terms of the C-C bond length in benzene. That the deviations from linearity are probably not due to solvent effects is made clear by the fact that a plot of $\log K_X/K_H$ of the spiranes vs $\log K_X/K_H$ for meta-substituted benzoic acids produces similar scatter (Figure 3) (51,52). Closer inspection of Figure 2 reveals that most of the deviations are in the same direction as the resonance contribution of the substituent. Stock and Holtz have made similar observations in attempting to correlate the pKa's of the bicyclo[2.2.2]octanes with $\sigma_{1,4}$ parameters (13). It appears that a saturated system would make a more satisfactory choice as a model for the field effect since π -inductive and mesomeric effects seem to

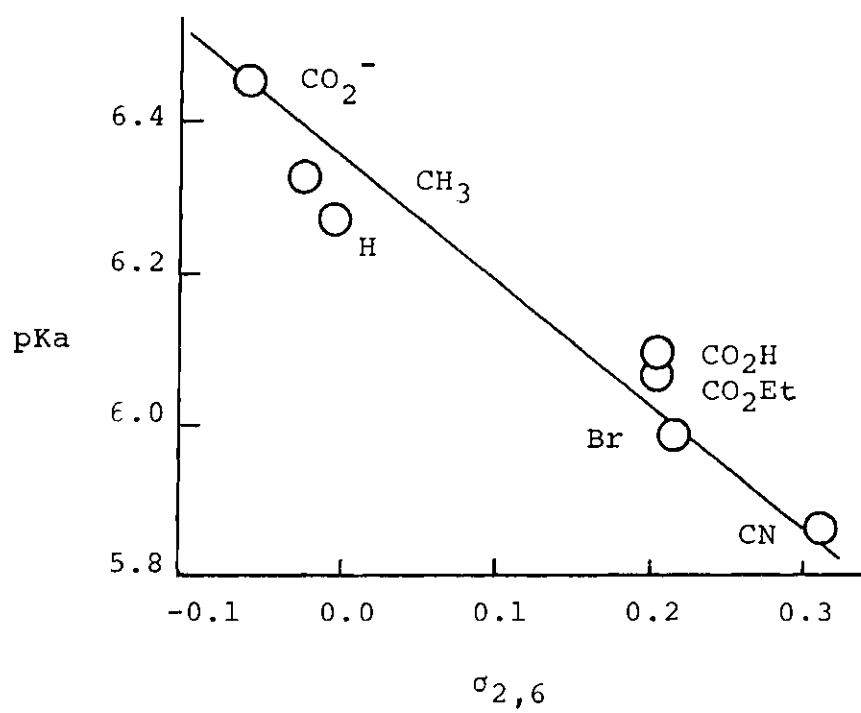


Figure 2. Correlation of pKa with $\sigma_{2,6}$

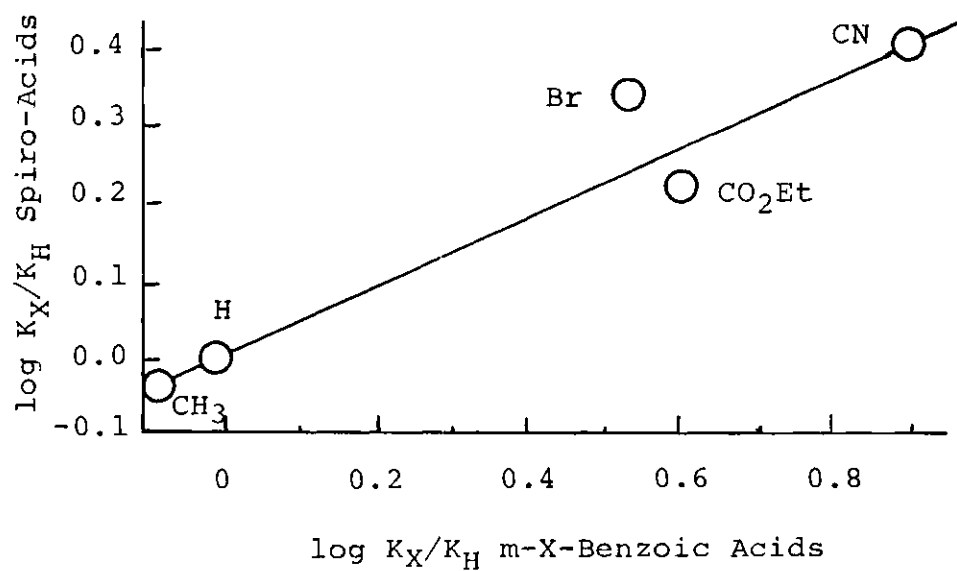


Figure 3. Correlation of $\log K_X/K_H$ Spiro-Acids with $\log K_X/K_H$ m-X-Benzoic Acids

be operative in meta-substituted benzoic acids (1,13,24 53,54).

Field Effect

Empirical approaches to quantitatively describe non-conjugative substituent effects are successful to varying degrees with the spiro acids. The theoretical approach based on the electrostatic interaction of a substituted dipole or charge with the reaction center will be examined next.

The most successful treatments of this type have been based on the Kirkwood-Westheimer cavity model with the modifications as proposed by Tanford (5,6,7,8,11). The equation usually employed to calculate the ratio of the dissociation constants of substituted acids relative to the parent acid is as follows:

$$\log K_X/K_H = \frac{e\mu \cos \theta}{2.3 kTR^2\epsilon_{De}} \quad , \quad (2)$$

where μ is the group or bond moment relative to hydrogen, R the distance from the center of the dipole to the ionizable proton, θ the angle between R and the substituent dipole axis, and ϵ_{De} the "effective" dielectric constant. All other symbols have their usual meaning.

In order to examine the spiro acids by equation 2, a knowledge of the parameters R and θ is necessary. It has been shown that cyclobutane rings may be planar or puckered, the trans isomer of cyclobutane-1,3-dicarboxylic acid being planar in the solid state (55), while the cis isomer has a dihedral angle of 149° (56). In solution a dihedral angle of 149° has been found for a variety of cyclobutane derivatives by means of dipole moment and nmr analyses (57,58). Due to the uncertainty in conformation of the four-membered rings, calculations have been carried out on what are considered to be the two extremes, planar and bent with an angle of 149° .

The calculations were carried out using three dimensional vector analysis and trigonometry. The bond lengths used in the calculations were 1.54 \AA for C-C bonds and 1.09 \AA for C-H bonds. The bond angles for external H-C-X were 112° while ring C-C-C angles were taken as 90° . The lengths of dipoles were considered to be standard C-X bond distances when X was a single atom. When X was a group of atoms, the dipole length was considered to be the maximum extension of the group as projected on the C-X bond axis. The dipole lengths used were: C-H (1.09 \AA), C-CN (2.62 \AA), C-Br (1.94 \AA), C-CH₃ (1.71 \AA), and CO₂R (2.99 \AA). The

position of the ionizable hydrogen was fixed at 1.45 \AA beyond the carboxyl carbon on the extension of the C-C bond in accordance with the suggestion of Kirkwood and Westheimer (5).

Bond or group moments were assessed from data tabulated by Smyth (59) for the dipole moments of substituted methanes in benzene solution. It is suggested that these values be used as they present a better interpretation than values taken from gas phase measurements (59). It has been assumed that the bond moment of the C-H bond is 0.4 with hydrogen as the negative terminus (6). Smyth devotes considerable discussion to this point and concludes that popular opinion supports 0.4 as the magnitude but that controversy rages over the direction.

The effective dielectric (ϵ_e) was calculated for both conformations by the spherical and ellipsoidal cavity models of Kirkwood and Westheimer (5,6,7,8) assuming an external dielectric of 49.5 and an internal dielectric of two. The center of the dipole and the ionizable proton were placed 1.5 \AA below the surface of the cavity according to the suggestion of Tanford (11). This procedure fixes the cavity dimensions so that the effective dielectric may be calculated from the tabulations of Westheimer, Jones and Lad (7).

The results of the $\log K_X/K_H$ calculations and parameters are summarized in Tables 3 and 4. Clearly both extremes in conformation lead to very similar results. This is a case in which there is partial compensation between R and $\cos \theta$. As one proceeds from a planar structure to a bent structure the distance R increases and so does the \cos of θ . Excellent agreement of the calculated $\log K_X/K_H$ ratios with the experimental values is found with the spherical cavity model for both the planar and bent structures. The ellipsoidal cavity model in both cases results in $\log K_X/K_H$ values which are far below the experimental values found. This model appears to over estimate the value of De . A similar situation was found by Stock and Holtz (13).

Table 5 shows the calculations of $\log K_1/4K_2$ for spiro[3.3]heptane-2,6-dicarboxylic acid by use of Equation 1,

$$\log K_1/4K_2 = \frac{e^2}{2.3 kTRDe} , \quad (1)$$

where all symbols have their usual significance. It may be seen that the puckered ellipsoidal model gives a ratio much closer to the one experimentally determined than the spherical models. This result is difficult to explain in view of the fact that the spherical model gives by far the best

Table 3. Parameters and Calculated Values for $\log K_X/K_H$ of 6-X-Spiro[3.3]-heptane-2-carboxylic Acids^a at 25°C by Equation 2

Sub	Parameters		θ°	Tanford Sphere		Tanford Ellipse		Exp. $\log K_X/K_H$
	R, Å	$\mu_X D$		De	$\log K_X/K_H$	De	$\log K_X/K_H$	
H	6.82	0.40	56°14'	4.80	0.00	9.88	0.00	---
CN	7.27	3.90	50°36'	5.02	0.42	10.19	0.21	0.41 ± 0.03
Br	7.07	2.20	52°12'	4.90	0.23	10.15	0.11	0.28 ± 0.03
CO ₂ C ₂ H ₅	7.41	2.26	48° 8'	5.21	0.22	11.08	0.10	0.20 ± 0.04
CH ₃	7.00	0.00	52°58'	4.84	-0.05	9.96	-0.02	-0.06 ± 0.03
CO ₂ H	7.41	2.03	48° 8'	5.21	0.19	11.08	0.09	0.17 ± 0.03

^aPlanar cyclobutanes

$$e = 4.80 \times 10^{-10} \text{ esu}, \mu = \mu_X - \mu_H \times 10^{-18} \text{ esu/cm}, k = 1.381 \text{ erg/K}^\circ, T = 298^\circ\text{K}$$

Table 4. Parameters and Calculated Values for $\log K_X/K_H$ of 6-X-Spiro[3.3]-heptane-2-carboxylic Acids^a at 25°C by Equation 2

Sub	Parameters		θ°	Tanford Sphere		Tanford Ellipse		Exp. $\log K_X/K_H$
	R, Å	μ , D		De	$\log K_X/K_H$	De	$\log K_X/K_H$	
H	7.29	0.40	30°26'	5.08	0.00	10.19	0.00	---
CN	7.97	3.90	26°36'	5.61	0.45	12.38	0.20	0.41 ± 0.03
Br	7.66	2.20	28°18'	5.43	0.25	11.39	0.12	0.28 ± 0.03
CO ₂ C ₂ H ₅	8.14	2.26	26° 2'	5.75	0.22	12.60	0.11	0.20 ± 0.04
CH ₃	7.56	0.00	28°54'	5.33	-0.06	10.26	-0.03	-0.06 ± 0.03
CO ₂ H	8.14	2.03	26° 2'	5.75	0.19	12.60	0.10	0.17 ± 0.03

^aPuckered cyclobutanes 149° dihedral angle

Table 5. Parameters and Calculated Values for
 Log $K_1/4K_2$ for Spiro[3.3]heptane-2,6-
 dicarboxylic Acid at 25°C

	$\overset{\text{O}}{\text{RA}}$	De	log $K_1/4K_2$ calcd.	log $K_1/4K_2$ exp.
planar sphere	8.46	37.58	0.76	0.35
planar ellipse	8.46	58.54	0.49	0.35
puckered sphere	9.51	42.37	0.61	0.35
puckered ellipse	9.51	60.40	0.42	0.35

results for the dipolar substituted spiro acids. Indeed the spherical cavity model gives excellent results for the 1,4-diacids of the bicyclo[2.2.2]octane, bicyclo[2.2.2]octene and cubane systems (14).

Stock and Holtz (13) have proposed that equation 2 be modified in recognition of the fact that R , θ , and De of the parent acid are usually quite different from these parameters in most dipolar substituted acids and that $\log K_X/K_H$ ratios might be more realistically calculated by equation 3,

$$\log K_X/K_H = \frac{e}{2.3kT} \left[\left| \frac{\mu \cos \theta}{R^2 De} \right|_X - \left| \frac{\mu \cos \theta}{R^2 De} \right|_H \right], \quad (3)$$

where each symbol has its usual significance. The results of this calculation are shown in Table 6. The $\log K_X/K_H$ ratios are essentially the same as those obtained from the original formulation of the electrostatic equation 2.

Discrepancies in calculated and experimental values for $\log K_X/K_H$ in the bicyclo[2.2.2]octane system led Stock (13) to contend that hydrogen and alkyl substituted acids exhibit anomalous behavior when compared to acids substituted with more polar groups. This was confirmed by the curvilinear relationship found in plots of $\mu \cos \theta/R^2$ vs pK_a . It was speculated that the lyophobic character of hydrogen and alkyl allowed the solvent continuum to begin

Table 6. Calculated Values of $\text{Log } K_X/K_H$ for
6-X-Spiro[3.3]heptane-2-carboxylic
Acids from Equation 3

	Planar Sphere $\text{log } K_X/K_H$	Puckered Sphere $\text{log } K_X/K_H$
H	0.00	0.00
CN	0.41	0.43
Br	0.23	0.24
$\text{CO}_2\text{C}_2\text{H}_5$	0.22	0.21
CH_3	-0.05	-0.06
CO_2H	0.19	0.18

closer to these substituents while the more lyophilic substituents would incorporate more solvent within the cavity resulting in the solvent continuum beginning further from the substituent. The Dewar-Grisdale model (1) would suggest that the greater solvent interaction with lyophilic substituents tends to decrease the magnitude of the negative end of the dipole. Solvent influence on the hydrogen and alkyl would of course be much less.

Plots of pK_a vs $\mu \cos \theta / R^2$ for planar and bent conformations of the spiro acids are shown in figures 4 and 5. However no curvilinear relationship is evident. Indeed least squares analysis indicate values for D_e of 4.83 and 5.44 in remarkable agreement with the average values of 4.91 and 5.49 as calculated by the Tanford model. This independent assessment of D_e suggests that the model may be more reliable than has been the general view.

Comparison of Field and σ -Inductive Effects

In order to more fully examine the question of which model, field or σ -inductive most adequately describes the transmission of non-conjugative substituent effects, a comparison between the spiro acids (A) and both the 4-X-bicyclo[2.2.2]octane-1-carboxylic acids (B) and the 4-X-bicyclo[2.2.1]heptane-1-carboxylic acids (C) was made (60).

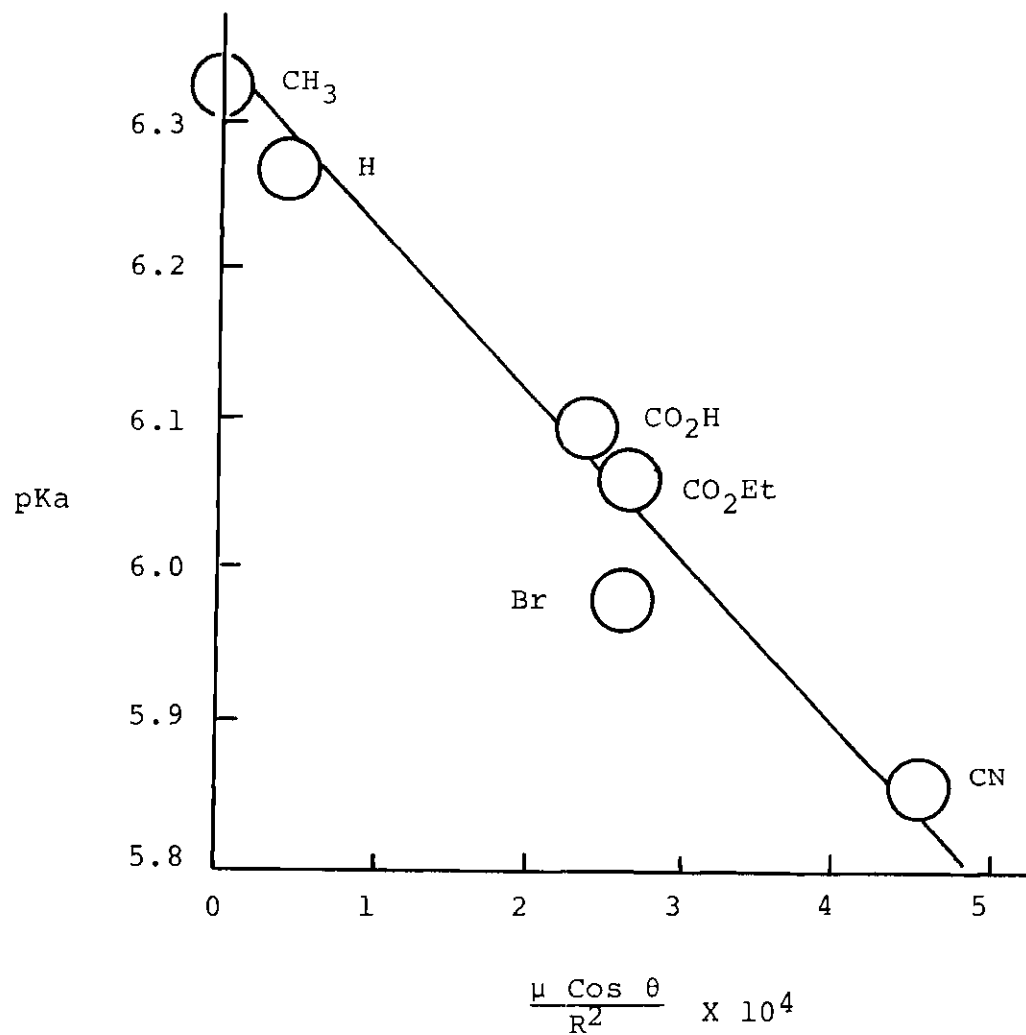


Figure 4. Correlation of pKa Spiro Acids with,
 $\frac{\mu \cos \theta}{R^2}$ for Planar Cyclobutanes

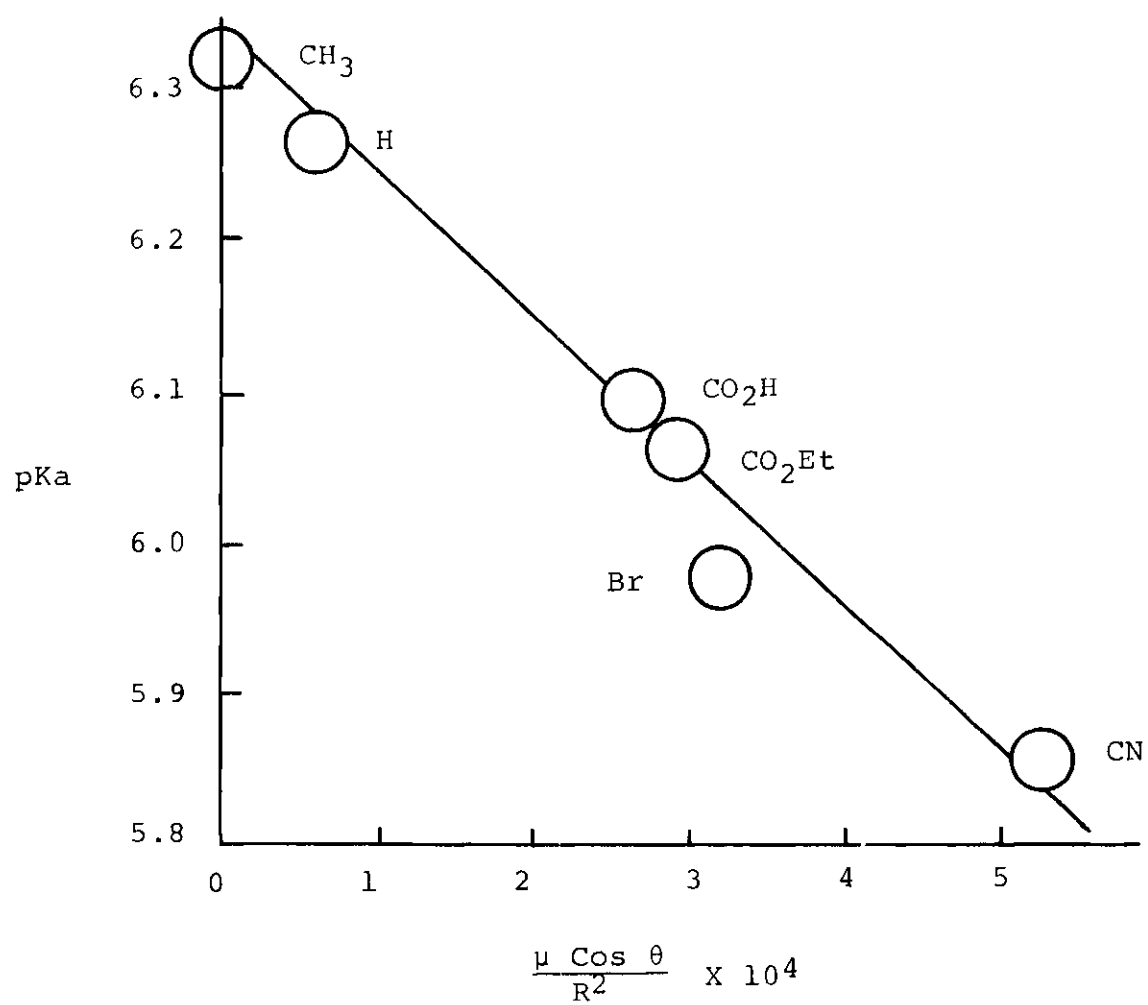
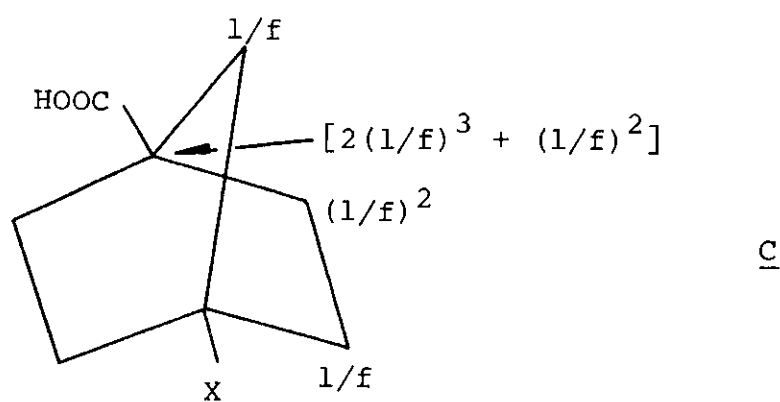
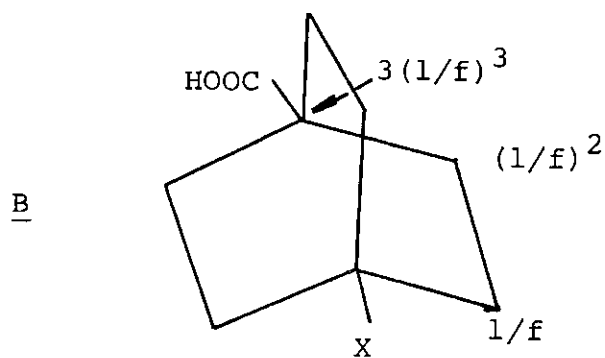
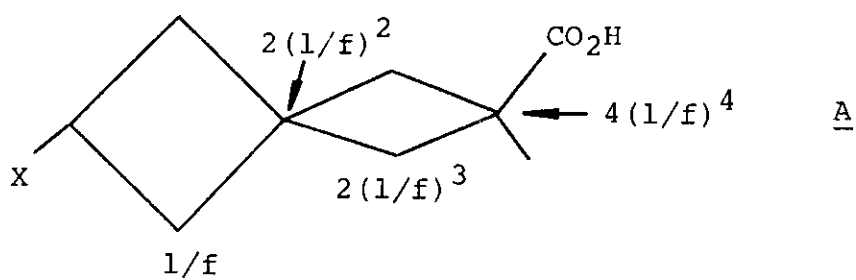


Figure 5. Correlation of pKa with $\frac{\mu \cos \theta}{R^2}$ for Puckerred Cyclobutanes

(See diagram 1.) The relative ability to transmit substituent effects was compared by plotting experimental pKa values for the bicyclooctanes in 50 percent (weight) aqueous ethanol vs the pKa values for the corresponding spiro acids (Figure 6). An excellent linear correlation was obtained with a slope or ρ/ρ_0 value of 2.12. Unfortunately the pKa values of the bicycloheptane acids in aqueous ethanol have not been reported. Wilcox and Leung, however have compared the acidities of systems B and C in water, 25 percent methanol-water and 50 percent methanol-water and have calculated slopes or ρ/ρ_0 values of bicycloheptane to bicyclooctane of 1.175, 1.183, and 1.195 respectively (17). A plot of ρ vs $1/D$, where D is the dielectric of the solvent, produces a straight line, which, when extrapolated to the $1/D$ value for 50 percent (weight) aqueous ethanol ($D = 49.5$) gives a ρ value of 1.210 (61). The "experimental ρ " in comparison of C to A is then calculated to be 2.56 ($B/A \times C/B = C/A$).

Theoretical ratios for the field model may be calculated by dividing $\cos \theta/R^2 \epsilon$ for each acid in systems B and C by the same factor for the corresponding spiro acid. In each case the value of ϵ was assessed by the Tanford modification using a spherical cavity.

DIAGRAM 1



pKa Bicyclic Acids

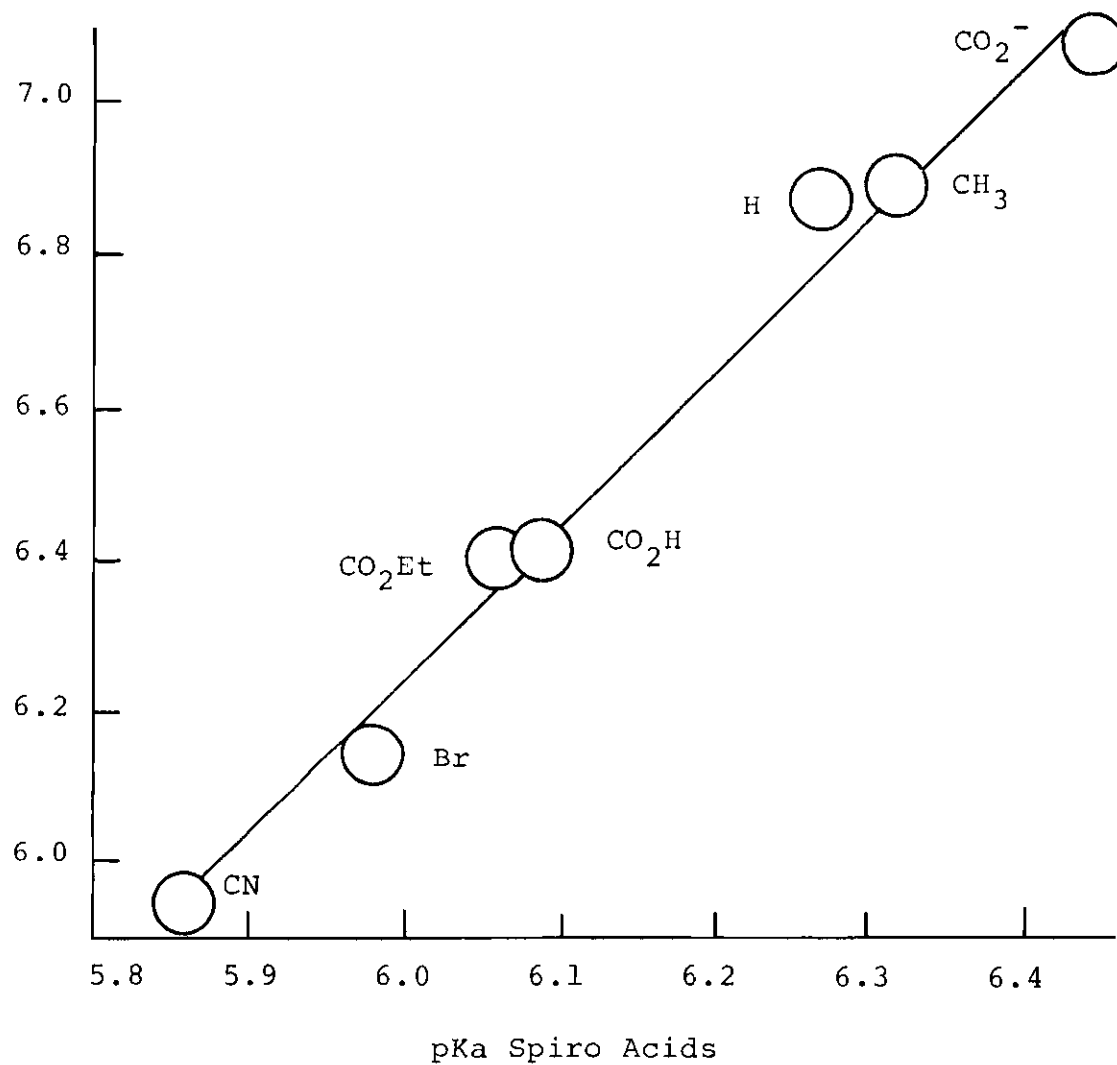


Figure 6. pKa's Bicyclo[2.2.2]octanes Acids
vs pKa's Spiro Acids

The average slope predicted in comparing the bicyclo-octane to the spirane was found to be 2.01 ± 0.14 and for the bicycloheptanes to spiranes 2.40 ± 0.07 .

The method for predicting theoretical slopes from the inductive model may be seen by referring to diagram 1 and equations 15 and 16.

$$B/A = 3(1/f)^3/4(1/f)^4 = 3f/4 \quad (15)$$

$$C/A = [2(1/f)^3 + (1/f)^2]/4(1/f)^4 = [2f + f^2]/4 \quad (16)$$

Fall-off factors of two and three were used (21,23, 47,62) leading to predicted slopes of 1.50 to 2.25 in comparing B to A and 2.00 to 3.75 in comparing C to A. This data is summarized in Table 7. Wilcox and Leung have suggested $f = 2.7$ is the most reasonable fall-off factor. Using this value the ratio B/A is 2.02, very close to both the experimental and field slopes in comparison of system B to A. This same fall-off factor, however, predicts a slope for systems C and A of 3.17 which is rather far from both the field and experimental slopes. These results strongly suggest that the field effect is a more useful approach in predicting the relative magnitude of substituent effects.

In order to avoid possible confusion it is desirable

Table 7. Experimental and Theoretical ρ -Values in the Comparison of Spiro[3.3]heptane (A), Bicyclo[2.2.2]octane (B), and Bicyclo[2.2.1]heptane Acids (C)

	B-A	C-A
Slope ρ (exp)	2.12	2.56
Slope ρ (TMKW)	2.01	2.40
Slope ρ (inductive) f = 2 to 3	1.50-2.25	2.00-3.75
Slope ρ (inductive) f = 2.7	2.02	3.17
Slope ρ (inductive) f = 2.1	1.75	2.15

to stress what the present results do not demonstrate. It may be suggested that there are inductive models alternate to the simple one implied in diagram 1 and equations 15 and 16. For example the bicyclooctane and bicycloheptane systems have orbitals properly aligned for overlap as proposed by Hoffman (78). Clearly the fall-off factor which adequately predicts the ability to transmit substituent effects in one system may not be the proper one to use in some other system. The differences in hybridization of atoms in the hydrocarbon framework could alter the polarizabilities of the atoms and their connecting bonds.

σ -Inductive Effect

In order to find the best fall-off factor for the spiro heptane system the method of McGowan (21) for evaluating inductive effects was used as shown in equation 7.

$$-2.3 \text{ RT } \log K_X = -2.3 \text{ RT } \log K_H - BQ, \quad (7)$$

where B is $(1/f)^n$ times the number of different pathways from substituent to reaction center times 14, and Q is the effective charge of a substituent group as determined from the ionization constants of substituted acetic acids. The fall-off factor is f and n is the number of bonds between the point of attachment of the substituent group and the

oxygen to which the ionizable proton is attached. The number 14 is the effect in kcals of a full formal charge at the oxygen to which the proton is attached. All other symbols have their usual significance. Table 8 shows the calculated values for the pKa's of the spiro acids using several different fall-off factors. A fall-off factor of 2.1 gives the best agreement with experimental results.

Using 2.1 as the fall-off factor in equations 15 and 16 gives slopes of 1.75 and 2.15 respectively in comparing systems B and C to A. What may be clearly stated is that the simple traditional inductive model does not work in comparing several different systems. The spiro acids seem to be excellent models for evaluation of the field effect. The next section of this thesis will deal with systems wherein the hydrocarbon framework of several molecules remains constant while parameters determining field effects are varied.

Table 8. Calculated Values of pKa for 6-X-Spiro[3.3]-heptane-2-carboxylic Acids by the Inductive Model, Equation 7^a

Sub	Q	pKa (f = 2)	pKa (f = 2.7)	pKa (f = 2.1)	pKa (exp)
CN	0.90	5.960	6.173	5.838	5.856
Br	0.63	5.863	6.200	5.968	5.980
CO ₂ C ₂ H ₅	0.60	5.882	6.203	5.981	6.062
CO ₂ H	0.57	5.901	6.206	5.996	6.096
CO ₂ ⁻	-0.43	6.368	6.283	6.471	6.450
CH ₃	-0.11	6.336	6.277	6.321	6.321

^aThere are six bonds and four pathways.
 $R = 1.99 \times 10^{-3}$ kcal/mole deg.

CHAPTER V

CONCLUSIONS - SECTION I

The 6-substituted spiro[3.3]heptane-2-carboxylic acids are shown to give excellent correlation between theoretical values of $\log K_X/K_H$ as predicted by the Tanford modification of the Kirkwood-Westheimer equation and experiment.

They also show by comparison to other saturated systems that the field model is better able to predict the relative abilities of saturated systems to transmit substituent effects than is the simple σ -inductive effect model.

CHAPTER VI

EXPERIMENTAL - SECTION II

Preparation of Bridge Substituted Bicyclo-
[2.2.2]octane-2-carboxylic Acids and Esters

The preparation of bridge substituted bicyclo[2.2.2]-octane-2-carboxylic acids is outlined in schemes III and IV.

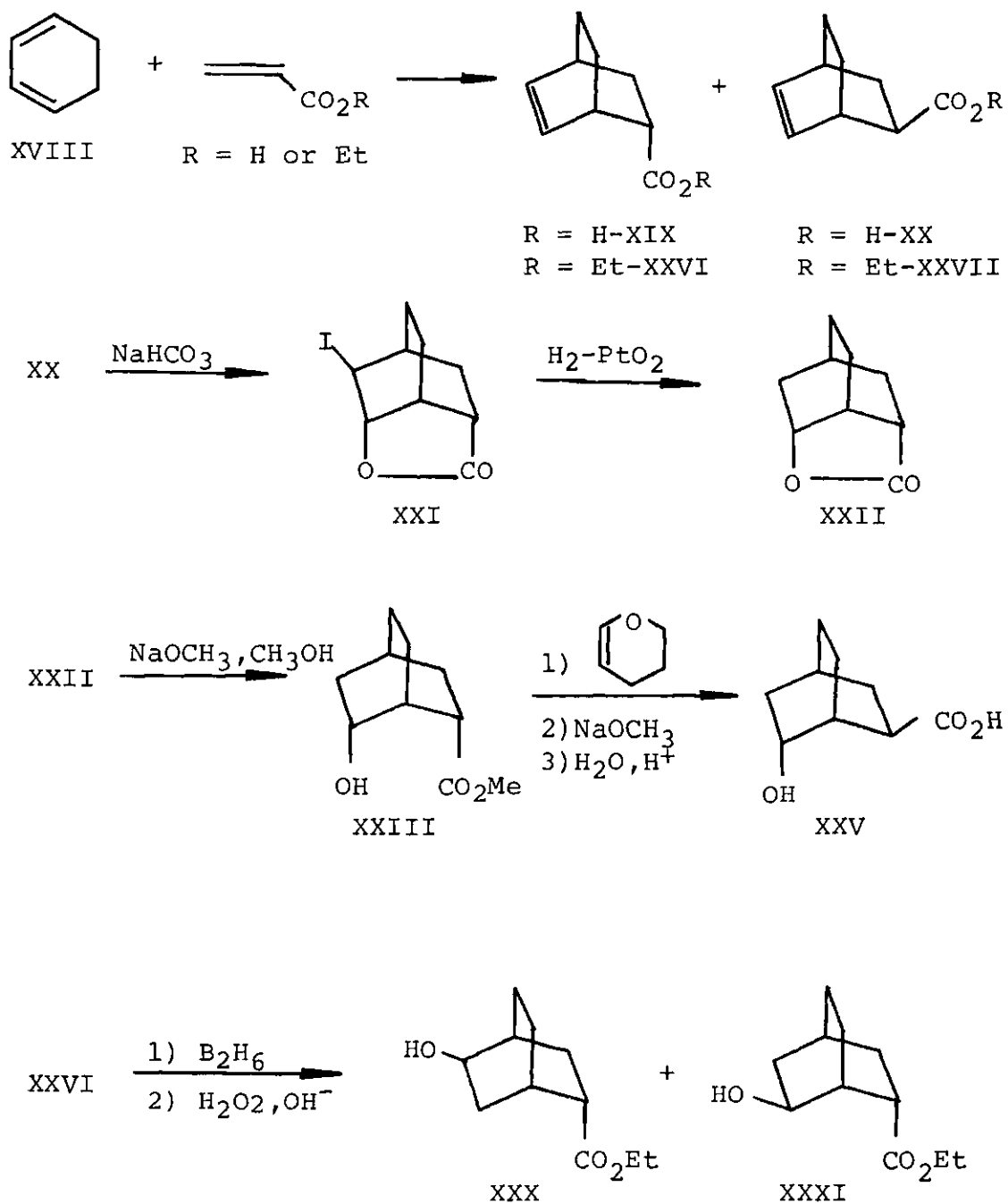
1,2-Dibromocyclohexane (XVII)

Following a previously described procedure (63), a three-necked, three liter round bottom flask, equipped with a magnetic stirrer, dropping funnel, and thermometer was charged with 500 g of cyclohexene and cooled in a dry ice-acetone bath. Liquid bromine was added from the dropping funnel so that the temperature of the reaction remained below 0°C. Addition was stopped when a definite bromine color persisted. The product was kept dark and cold after distillation at reduced pressure, as exposure to light seems to cause rapid decomposition.

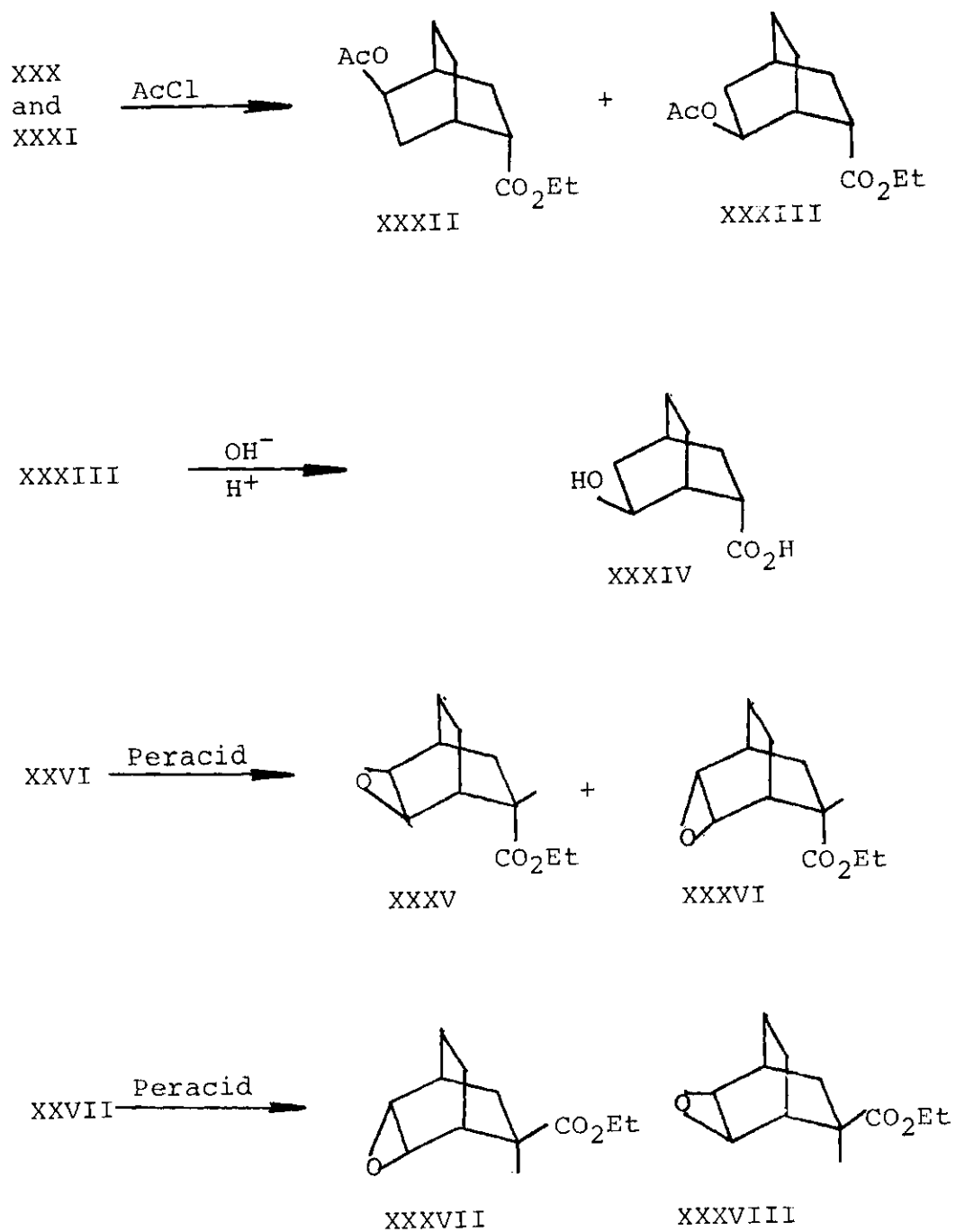
1,3-Cyclohexadiene (XVIII) (63)

A three-necked, two liter round bottom flask, equipped with a dropping funnel, a ground glass stirrer, a thermometer, and a fractionating column and distilling head

SCHEME III



SCHEME IV



was charged with 500 ml of ethylene glycol and 250 g of sodium hydroxide. The mixture was heated to 220°C and dibromocyclohexane (333 g) was slowly dropped into the hot solution at such a rate that the temperature of the distilling head remained below 100°C. The distillate consisted of a water layer and an organic layer. The organic layer was dried over magnesium sulfate and distilled in small lots. The fraction boiling at 78-81°C contained 75 percent 1,3-cyclohexadiene as determined by glc (SE-30-50°).

Exo-endo Mixture of Bicyclo[2.2.2]oct-2-ene-5-carboxylic Acid (XIX) (XX)

Following a known procedure (64), 24.6 g (0.31 mole) commercial 1,3-cyclohexadiene, 30.4 g (0.42 mole) acrylic acid and 0.25 g of hydroquinone were sealed in a heavy walled glass ampoule under a blanket of nitrogen. The vessel was heated at 175°C for 24 hours in a steel bomb. The mixture was evacuated by aspirator to remove low boiling starting materials. Distillation at reduced pressure yielded a fraction of b.p.₃ 117-130°C (lit. b.p.₂₀ 140-150°C) which solidified on setting. The semisolid mass was recrystallized from n-hexane at -30°C yielding 13.6 g (30 percent) of white solid mixture of XIX and XX, m.p. 41-48°C. Neither isomer was isolated in a pure state from

this procedure and the mixture was used as is in subsequent steps.

5-Iodo-6-endo-hydroxybicyclo[2.2.2]octane-2-endo-carboxylic
Acid Lactone (XXI)

Iodolactone XXI was prepared by the general procedure of Van Tamelen (65) with all operations being performed in the dark since the compound deteriorates rapidly in light. The exo-endo mixture of bicyclo[2.2.2]oct-2-ene-5-carboxylic acid (4.5 g; 0.030 mole) was dissolved in 180 ml of 0.5 M sodium bicarbonate to which 15.8 g of iodine and 29.0 g of potassium iodide dissolved in 90 ml water were added. The reaction mixture was kept in the dark and stirred overnight at room temperature. The stirring was stopped and the mixture allowed to settle. The supernatant solution was poured off and the black oil in the bottom of the flask dissolved in chloroform. The chloroform was decolorized by shaking with aqueous sodium thiosulfate solution, washed with 10 percent sodium bicarbonate solution and then washed with water. The organic layer was dried over magnesium sulfate and the chloroform removed in vacuo. The yellow residue was recrystallized from n-hexane yielding 4.3 g (52.5 percent) of white crystalline XXI of m.p. 80-81°C (lit. 81-82°C) (64,66). $\nu_{\text{max}}^{\text{KBR}}$ 3000, 1790, 1460 cm^{-1} .

6-Endo-hydroxy Bicyclo[2.2.2]octane-2-endo-carboxylic Acid
Lactone (XXII)*

Iodolactone XXI (4.0 g; 0.0145 moles), 1.6 g triethyl amine (0.0145 mole), and 0.24 g of platinum oxide in 50 ml of ethyl acetate were treated with hydrogen at 40 psi on a Parr shaker for seven hours at 28°C. The triethylammonium hydroiodide was filtered off and the ethyl acetate removed in vacuo. The residue was recrystallized from n-hexane and sublimed at reduced pressure to yield 1.3 g (60 percent) white crystals of XXII, m.p. 205-206°C (lit. 207-208°C) (64,66); $\nu_{\text{max}}^{\text{KBr}}$ 2940, 2880, 1770 cm^{-1} ; nmr (DCCl_3) τ : 5.40 (m,1), 7.65 (m,1), 8.35 (m,9).

Methyl-6-endo-hydroxy Bicyclo[2.2.2]octane-2-endo-carboxylate
(XXIII)

Opening of the lactone is accomplished by dissolving 4.0 g (0.026 mole) XXII in 80 ml of 0.70 N sodium methoxide in dry methanol and refluxing for one hour. The methanol was concentrated to one-half volume in a stream of air. Concentrated hydrochloric acid (5.30 ml) in 120 ml of ice water were then added to the mixture. The solution was

* All attempts to prepare lactone XXII directly from the bicyclooctene acid mixture by treatment with sulfuric acid (64) led to yields of less than ten percent.

extracted with seven-50 ml portions of chloroform and the chloroform allowed to evaporate in the hood. The solid was washed with two-12 ml portions of hexane to remove lactone and the residue was recrystallized from cold methanol by the addition of water. The white powder was air dried yielding 3.4 g (71 percent) of hydroxy ester XXIII, m.p. 112-115°C; $\nu_{\text{max}}^{\text{KBr}}$ 3400, 2920, 1690 cm^{-1} . At 115°C the liquid bubbled vigorously and forms a solid, m.p. 201-204°C indicating formation of lactone XXII by loss of methanol and confirmed by ir (γ -lactone peak at 1770 cm^{-1}). It was also found that lactonization through loss of methanol occurred spontaneously in the dry powder at room temperature and that the hydroxy ester must be prepared and used in the same day.

Methyl-6-endo-(2-oxytetrahydropyran)bicyclo[2.2.2]octane-2-endo-carboxylate (XXIV)

Dihydropyran (40 ml) containing a small crystal of paratoluenesulfonic acid was cooled to 0°C in an ice bath. Slowly, 4.0 g of hydroxy ester XXIII was added to the solution. The slurry which formed was stirred 45 minutes at 0°C at which time it turned clear. Stirring was continued 15 additional minutes followed by the addition of 0.3 g sodium bicarbonate. The solution was filtered and the excess dihydropyran removed in vacuo. The oil which

remained was not further purified but infrared analysis showed the complete absence of any OH peak at 3400 cm^{-1} and the presence of an ester carbonyl at 1720 cm^{-1} . A small peak at 1770 cm^{-1} indicated that some lactone had formed in the course of the reaction.

6-Endo-hydroxy Bicyclo[2.2.2]octane-2-exo-carboxylic Acid
(XXV)

Epimerization of the methyl-2-endo-carboxylate XXIV was carried out by adding 25 ml of dry methanolic 0.7 N sodium methoxide to the oil XXIV. This mixture was allowed to stir at 28°C for five days. One-half the methanol was removed in vacuo, the solution diluted with 50 ml of ice water and acidified with cold 1.0 N hydrochloric acid. The aqueous solution was extracted with six-50 ml portions of ether, the ether layers combined, dried over magnesium sulfate and evaporated in vacuo.

The oily residue was refluxed with 1.0 g of sodium hydroxide in 20 ml of 95 percent ethanol for two hours. The reaction mixture was cooled, diluted with 50 ml of water and extracted with three-50 ml portions of ether to remove any unreacted esters. The water layer was acidified to pH one with 1.0 N hydrochloric acid and stirred for two hours at room temperature to remove the dihydropyran

blocking group. The water layer was extracted with ether for a 24 hour period, the ether dried over magnesium sulfate and removed in vacuo leaving a sticky white solid. Infrared indicated the presence of some lactone XXII. Purification was effected by column chromatography on 20 g of silica gel. Lactone XXII was eluted by 150 ml of benzene. A solution of 40 percent methanol-benzene eluted solid hydroxy acid XXV. Sublimation at 60°C and 2.5 mm yielded 0.47 g (10.5 percent) hydroxy acid XXV, m.p. 136.5-138°C. Neutralization equivalent calculated for $C_9H_{14}O_3$: 170.20. Found: 170.80; $\nu_{\text{max}}^{\text{KBr}}$ 3500-2500, 1690, 1370 cm^{-1} ; mass spectrum (70 ev) no m/e beyond 152 (loss of H_2O), 100 percent at 80.

Ethyl Bicyclo[2.2.2]oct-2-ene-5-endo-carboxylate (XXVI) and Ethyl Bicyclo[2.2.2]oct-2-ene-5-exo-carboxylate (XXVII)

Using a previously described procedure (67), 68.0 g (0.85 mole) of 1,3-cyclohexadiene and 109.0 g (1.09 mole) of ethyl acrylate were sealed under nitrogen in thick walled glass ampoules and heated in a steel bomb at 180°C for 12 hours. The mixture was evacuated by aspirator to remove low boiling starting materials. Glc (carbowax, 105°C) indicated a composition of 15 percent exo XXVII and 85 percent endo XXVI esters. Distillation on a spinning band column gave

partial separation of the isomers. The fraction b.p._{0.3} 38-46°C had 6.0 g with approximately 50 percent exo, 20 percent endo, and 30 percent unknown materials; fraction b.p._{0.3} 46-52°C contained 55.8 g of 18 percent exo and 82 percent endo; fraction b.p._{0.3} 52-54°C contained 29.8 g of 98 percent endo. Overall yield was 59 percent.

Complete separation of the isomers was achieved by silica gel chromatography on a 97 X 2.5 cm column using 15 percent benzene-85 percent cyclohexane as elutant; the exo isomer being eluted first.

In a typical separation 10.2 g of the mixture containing 30 percent exo-70 percent endo (enriched by distillation) is eluted in 100 ml fractions. The first 37 fractions contained nothing. At fraction 38 the distinct odor of the ester was noticed as well as visual changes in the index of refraction of the solvent. Selected fractions were evaporated and monitored by glc. Pure benzene was added to the column at fraction 60. Fraction 67 showed traces of endo isomer. Fractions 38 through 66 were combined, evaporated and found contained 3.1 g of pure exo isomer XXVII. Fraction 70 showed pure exo isomer. Fractions 67-69 had 0.5 g of mixed ester. Continued elution with pure benzene to fraction 90 produced 6.6 g of pure endo isomer XXVI.

Ethyl bicyclo[2.2.2]oct-2-ene-5-exo-carboxylate XXVII was distilled, b.p._{0.9} 70-71°C (lit. mixture b.p.₁₂ 98-100°C) (67); $\nu_{\text{max}}^{\text{neat}}$ 3040, 2950, 2870, 1730, 1610, 1465, 1370 cm^{-1} ; nmr (neat) τ : 3.90 (m,2), 6.10 (q,2), 9.0 (t,3) and a complex structure between 7.2 and 8.8 distinct peaks at 7.4, 7.7, 8.55, 8.7 integrating to 9 protons.

Ethyl bicyclo[2.2.2]oct-2-ene-5-endo-carboxylate XXVI was distilled; b.p._{0.35} 55°C (lit. mixture b.p.₁₂ 98-100°C) (67); $\nu_{\text{max}}^{\text{neat}}$ 3040, 2940, 2870, 1730, 1610, 1450, 1370 cm^{-1} ; nmr (neat) τ : 3.90 (m,2), 6.10 (q,2), 7.2 (m,1), 7.55 (m,2), 8.35-8.80 (m,6), 8.95 (t,3).

Bicyclo[2.2.2]oct-2-ene-5-exo-carboxylic Acid (XIX)

Saponification of 0.72 g (0.004 mole) of exo-bicyclo-octene ester XXVII was accomplished by refluxing for three hours with four milliliters of a 50 percent aqueous ethanol solution of 2.0 N sodium hydroxide. Four ml of water were added and the solution extracted with two-20 ml portions of ether to remove unreacted ester. The solution was cooled to 0°C and acidified with four ml of cold 2.0 N hydrochloric acid. The white precipitate was filtered and the water layer extracted with four-20 ml portions of ether to remove dissolved acid. The ethereal extract was dried over magnesium sulfate and evaporated in vacuo. The solid

fractions were combined and sublimed at 35°C, 0.4 mm, to yield 0.42 g (69 percent) of exo acid XIX, m.p. 49-50°C (lit. 46-47°C) (64). Neutralization equivalent: calcd. 152.20, found 152.24; $\nu_{\text{max}}^{\text{nujol}}$ 3500-2500 (broad), 1700, 1610 cm^{-1} ; nmr τ : -1.00 (s,1), 4.20 (m,2), 7.70 (m,1), 8.00 (m,2), 8.3-9.5 (m,6); mass spectrum shows a parent ion peak at m/e 152 and a 100 percent peak at 80.

Bicyclo[2.2.2]oct-2-ene-5-endo-carboxylic Acid (XX)

Saponification of 2.93 g (0.016 mole) endo ester XXVI was carried out by refluxing in 16 ml of 2.0 N sodium hydroxide in 50 percent ethanol for three hours. Then 16 ml of water were added to the reaction mixture and it was extracted with two-80 ml portions of ether to remove starting material. The mixture was cooled to 0°C and acidified with 16 ml of cold 2.0 N hydrochloric acid. The cloudy mixture was extracted with five-60 ml portions of ether, the extract dried over magnesium sulfate and evaporated in vacuo. The solid was sublimed at 35°C, 0.4 mm, to yield 1.54 g (63 percent) of white crystalline endo acid XX, m.p. 59-60°C (lit. 56-57°C) (64). Neutralization equivalent: calcd. 152.20, found 152.25; $\nu_{\text{max}}^{\text{KBr}}$ 3500-2500, 1700, 1610 cm^{-1} ; nmr (DCCl_3) τ : -2.00 (s,1), 3.80 (m,2), 7.10 (m,1), 7.40 (m,2), 8.35-8.90 (m,6); mass spectrum shows a parent ion peak m/4 152 and 100 percent peak at 80.

Bicyclo[2.2.2]octane-2-carboxylic Acid (XXVIII)

Hydrogenation of 2.98 g (0.0195 mole) mixture of XX and XIX was carried out at 747 mm and 33°C in 20 ml ethyl acetate with 0.043 g platinum oxide as a catalyst. The reaction took 455 ml of hydrogen (90 percent of theory) in four hours. The catalyst was filtered off, the solvent removed in vacuo, and the solid recrystallized from ten percent aqueous ethanol. Sublimation at 0.8 mm, 45°C, yielded 2.68 g (89 percent), saturated acid XXVIII of m.p. 83-84.5°C (lit. 84-85°C) (67). Neutralization equivalent: calcd. 154.22, found 154.09; $\nu_{\text{max}}^{\text{KBr}}$ 3500-2500 (broad), 1690, 1450, 1410 cm^{-1} ; nmr (DCCl_3) τ : -2.00 (s,1), 7.40 (m,1), 8.10-8.90 (m with large single spike at 8.50, 12).

The large singlet spike is due to four protons on the bridge away from the carboxyl group. The mass spectrum shows a parent ion peak at m/e 154 and the 100 percent peak is now at 137.

Ethyl Bicyclo[2.2.2]octane-2-carboxylate (XXIX)

Hydrogenation of 3.50 g (0.0194 mole) of a mixture of exo and endo esters XXVI and XXVII was carried out in ten ml of ethyl acetate using 0.078 g of platinum oxide at 747 mm and 32°C. The reaction consumed 494 ml of hydrogen (97 percent) in 75 minutes. The catalyst was filtered off

and the solvent removed in vacuo. Distillation yielded 3.17 g (91 percent) saturated ester XXIX, b.p._{3.4} 84°C (lit. b.p.₁₂ 102-103°C) (67); $\nu_{\text{max}}^{\text{neat}}$ 2980, 2940, 2860, 1730, 1450, 1370 cm^{-1} ; nmr (neat) τ : 6.00 (q,2), 7.60 (m,1), 8.00-8.80 (m with large singlet at 8.60, 12), 8.95 (t,3).

Ethyl 5- and 6-Exo-hydroxybicyclo[2.2.2]octane-2-endo-carboxylates (XXX) and (XXXI)

Hydroboration (68) of 19.00 g (0.105 mole) pure ethyl bicyclo[2.2.2]oct-2-ene-5-endo-carboxylate was accomplished by adding it to 25 ml of dried tetrahydrofuran in a three-necked, 100 ml flask fitted with a dropping funnel, rubber balloon and nitrogen inlet tube. Sodium borohydride (1.63 g) and 29 ml of dry tetrahydrofuran were added, the flask flushed with nitrogen and cooled to 0°C in an ice bath. Tetrahydrofuran (12 ml) containing 7.78 g of boron trifluoride dietherate was added from the dropping funnel over a 30 minute period. The mixture was stirred 90 minutes, allowed to warm to room temperature and stirred three days.

The mixture was cooled to 0°C and 3.5 ml of cold water added dropwise followed by 10.4 ml of 3.0 N sodium hydroxide. An equal volume (10.4 ml) of 30 percent hydrogen peroxide was added over a 30 minute period. The flask was

allowed to warm to room temperature and stirring was continued 90 minutes. The mixture was diluted with 100 ml of water and extracted with four-200 ml portions of ether. The ether extract was dried over magnesium sulfate and evaporated in vacuo. The hydroxy ester mixture was distilled; b.p._{0.35} 110-116°C yielding 20.5 g (98 percent) hydroxy esters XXX and XXI. Glc (SE-30, 160°C) showed one large peak with a very slight split and several very small ones. $\nu_{\text{max}}^{\text{neat}}$ 3400, 2940, 2870, 1730 cm^{-1} ; nmr (DCCl_3) showed two triplets and quartets at 8.8 and 6.1 respectively and what looks like a doublet at 5.0. A complex multiplet exists at 7.5 to 8.7. Ethyl 5- and 6-Exo-acetoxycyclo[2.2.2]octane-2-endo-carboxylates (XXXII) and (XXXIII)

The mixture of hydroxy esters (12.32 g; 0.065 mole) was acetylated in 40 ml of dry benzene to which 5.8 g of dry pyridine had been added. The solution was cooled in an ice bath and 5.80 g of acetyl chloride in ten ml dry benzene was added from a dropping funnel over a 15 minute period. The mixture was stirred 30 minutes, allowed to warm to room temperature, and was stirred one hour. Solid pyridine hydrochloride was filtered off and washed with dry benzene. The benzene was removed in vacuo and the liquid distilled b.p._{0.35} 101-103°C to yield 13.30 g (89 percent) acetates

XXXII and XXXIII. Glc analysis (SE-30, 170°C) showed two major peaks. Peak 1 (retention time 6.7 minutes) was present in 53 percent abundance, while peak 2 (retention time 8.2 minutes) was present in 47 percent.

Peak 2 was shown to have an identical retention time to the acetate of the major product of oxymercuration-demercuration on endo-bicyclooctene ester*. Since oxymercuration is believed to occur predominantly in the five position (69), peak 2 is believed to be the 5-acetate XXXII. Peak 1 corresponded to a minor peak from oxymercuration and is the 6-exo-acetate.

Separation of the acetates was accomplished by the gracious aid of the Continental Oil Company** by preparative glc on SE-30 at 170°C.

Separated 6-exo-acetate XXXIII showed $\nu_{\text{max}}^{\text{neat}}$ 2940, 2860, 1730, 1450, 1370 cm^{-1} ; nmr (DCCl_3) τ : 5.10 (m,1), 5.90 (q,2), 7.20-8.70 (m with sharp spike at 8.00), 8.90 (t,3). Mass spectrum parent ion m/e 240, 100 percent at 180 with other large peaks at 80 and 152.

* Private communication from C. L. Liotta and L. Slighton, Georgia Institute of Technology.

** Through the thoughtful aid of Drs. Kennedy and Lindler.

6-Exo-hydroxy Bicyclo[2.2.2]octane-2-endo-carboxylic Acid

(XXXIV)

Saponification of 1.50 g (0.0062 mole) ethyl-6-acetoxibicyclo[2.2.2]octane-2-carboxylate was accomplished by refluxing 24 hours in six ml of 2.0 N potassium hydroxide in ethanol. The mixture was diluted with 20 ml of water and extracted with three-20 ml portions of ether. The water layer was acidified with 2.0 N hydrochloric acid and extracted overnight with ether. The ether layer was dried over magnesium sulfate and evaporated in ether. The solid residue was sublimed at 130°C, 1.3 mm to yield 0.52 g (49 percent) white crystals, m.p. 150-150.5°C. Neutralization equivalent: calcd. 170.20, found 170.30; $\nu_{\text{max}}^{\text{KBr}}$ 3400-2500, 2960, 2870, 1700 cm^{-1} . The mass spectrum showed no peaks past m/e 152 with the 100 percent peak at 80.

That hydroxyl is exo is made clear by the fact that no lactones were found in view of the behavior of compound XXIII.

Ethyl-3-oxatricyclo[3.2.2.0^{2,4} exo]nonane-6-endo-carboxylate
(XXXV) and Ethyl-3-oxatricyclo[3.2.2.0^{2,4} endo]nonane-6-endo
carboxylate (XXXVI)

Pure ethylbicyclo[2.2.2]oct-2-ene-5-endo-carboxylate (20.0 g; 0.11 mole) in 50 ml of dry ether was added to

28.0 g m-chloroperbenzoic acid (85 percent assay) in 150 ml of dry ether at 0°C. This mixture was allowed to warm to room temperature and react 14 days.

The ether was washed with five-100 ml portions of ten percent sodium bicarbonate to remove benzoic acid. The ether was dried over magnesium sulfate and evaporated in vacuo. The crude epoxide is distilled, b.p._{0.5} 86-95°C, yielding 18.6 g (89 percent) clear liquid. Glc (carbowax, 140°C) indicated a 87-13 ratio exo to endo epoxide. Epoxidation with perphthalic acid (70) gave roughly a two to one ratio and perbenzoic acid (71) gave a 2.5-1 ratio.

Separation of the isomers was accomplished by column chromatography on silica gel using five percent methanol-benzene. Exo-epoxide eluted first followed by the endo.

Exo-epoxide XXXV was distilled, b.p._{1.25} 101-102°C; $\nu_{\text{max}}^{\text{neat}}$ 2940, 2880, 1730, 1470, 1370, 1180, 1040, 850 cm^{-1} ; nmr (neat) τ : 5.90 (q,2), 6.90 (m,2), 7.45 (m,2), 7.95 (m,1), 8.0-8.7 (m,6), 8.8 (t,3); mass spectrum shows parent ion m/e 196 and the 100 percent at 79.

The endo-epoxide-endo-ester XXXVI had b.p._{0.3} 99-101°C; $\nu_{\text{max}}^{\text{neat}}$ 2940, 2880, 1730, 1470, 1370, 1200, 1040, 855 cm^{-1} ; nmr (neat) τ : 5.95 (q,2), 6.90 (m,2), 7.45 (m,1), 7.90 (m,3), 8.50 (s,4), 8.85 (t,3); mass spectrum shows the parent ion at m/e 196 and the 100 percent peak at 59.

Ethyl 3-Oxatricyclo[3.2.2.0^{2,4} endo]nonane-6-exo-carboxylate
 (XXXVII) and Ethyl 3-Oxatricyclo[3.2.2.0^{2,4} exo]nonane-6-exo-
carboxylate (XXXVIII)

Epoxidation of 10.0 g (0.055 mole) of exo-bicyclo-octene ester XXVII with 14.0 g meta-chloroperbenzoic acid in 100 ml dry ether was accomplished in 14 days by the procedure outlined above. Distillation yielded 9.8 g (91 percent) of mixed epoxides XXXVII and XXXVIII, b.p._{1.3} 98-99°C. Glc (1,2,3 tris(2-cyanoethoxy)propane, 160°C) indicated the presence of 67 percent XXXVII (retention time, 19.2 min) and 33 percent XXXVIII (retention time, 22 min).

Separation was by preparative glc through the courtesy of the Continental Oil Company using 20 percent tcp on firebrick at 130°C. Small portions for analysis were obtained by glc by peak shaving using 25 percent carbowax 20-M at 120°C.

Endo-epoxide-exo-ester XXXVII had ν_{\max}^{neat} 2950, 2880, 1730, 1470, 1450, 1370, 1210, 1190, 1040 cm⁻¹; nmr (neat) τ : 5.95 (q,2), 6.90 (m,2), 7.50 (m,2), 7.95 (s,broad,1), 8.15-8.60 (m,2), 8.55 (s,4), 8.85 (t,3); mass spectrum shows parent ion m/e 196 and 100 percent at 78.

Exo-epoxide-exo-ester XXXVIII had ν_{\max}^{neat} 2940, 2880, 1730, 1470, 1370, 1190, 1035 cm⁻¹; nmr (neat) τ : 5.90

(q,2), 6.80 (m,2), 7.50 (m,2), 7.95 (m,1), 8.1-8.8 (m,6), 8.8 (t,3); mass spectrum shows parent ion m/e 196 and 100 percent at 95.

Attempted Preparations of the Acids of XXXV, XXXVI, XXXVII, and XXXVIII

Basic hydrolysis of compounds XXXVI, XXXVII, and XXXVIII with potassium hydroxide in 95 percent ethanol at room temperature led in all cases upon acidification to oily materials from which no acids could be purified either by crystallization or sublimation.

Exo-epoxy-endo acid has been reported in the literature (72) m.p. 129-131°C. One attempt produced this acid in small yield, m.p. 121-125°C. However the acid converts quantitatively in the solid to 5-exo-6-endo-dihydroxy-bicyclo[2.2.2]octane-2-endo-carboxylic acid γ -lactone XXXIX, m.p. 233-236°C (lit. 235-237°C) (72); $\nu_{\text{max}}^{\text{KBr}}$ 1775 cm^{-1} . Subsequent attempts to prepare the acid led to nearly quantitative yields of the hydroxy lactone.

Other Attempted Preparations of 6-Exo-hydroxybicyclo[2.2.2]-octane-2-endo-carboxylic Acid (XXXIV)

Both diborane reduction and hydrogenation of exo-epoxide-endo-ester XXXV were attempted (73). In each case glc indicated the presence of at least eight products with

the major one being hydroxy lactone XXXIX. Severe difficulties of separation and subsequent discovery of the simple and successful hydroboration procedure led to setting aside the work in these areas.

Measurements of the pKa's of Acids XIX, XX, XXVIII, and
XXXIV

The pKa's of the bicyclic octane and octene acids were measured in 50 percent (weight) aqueous ethanol at 25°C. All acids were sublimed immediately prior to measurement. The procedure used was exactly the same as that outlined for the spiro acids in Chapter III except that all solutions were 1.0×10^{-2} M in acid instead of 7.4×10^{-3} .

Measurement of the Rates of Alkaline Hydrolysis of the
Isomeric Epoxy Esters XXXV, XXXVI, XXXVII and XXXVIII and
the Saturated and Unsaturated Esters XXVI, XXVII, XXIX

Rates of alkaline ester-hydrolysis were measured in 50 percent (weight) aqueous ethanol at 25°C by the general procedure outlined by Siegel and Kormarmy (12).

The general procedure was as follows. Two solutions of sodium hydroxide were made up in 50 percent (weight) aqueous ethanol and shown by titration to a phenolphthalein end point using potassium acid phthalate as a standard to be

4.00×10^{-2} N and 2.00×10^{-2} N. Standard 3.88×10^{-2} N hydrochloric acid in water was prepared and standardized by titration. Sufficient weights of freshly distilled esters whose purity was checked by glc were dissolved in 50 percent (weight) aqueous ethanol to make a solution 4.00×10^{-2} M in ester.

Equal volumes of 4.00×10^{-2} N base and ester solution, which had been equilibrated at 25°C in a constant temperature bath, were mixed by pipetting the base into the ester. The timer was started when one-half the base was added. The mixture was shaken and returned to the constant temperature bath. At appropriate time intervals an aliquot of reaction mixture was withdrawn, quenched with an equal volume of 3.88×10^{-2} N hydrochloric acid and back titrated with 2.00×10^{-2} N base to a phenolphthalein end point. Time was recorded when the pipette of reaction mixture was one-half emptied into the acid solution. All reactions were carried out to at least 50 percent completion.

When the supply of available ester was severely limited (XXXVII and XXXVIII), the ester was weighed into the reaction vessel and ten ml of 2.00×10^{-2} N base added so that the ester concentration was also 2.00×10^{-2} M. Very little deterioration of precision was found upon going from reaction volumes of 200 ml to ten ml.

Calculations of Second-Order Rate Constants

In all cases the reaction solutions were made up so that the initial base and ester would be equal. For this situation the rate law is expressed by Equation 17 (74),

$$\frac{-dc}{dt} = kc^2 \quad (17)$$

where c is the concentration of one of the reactants and k is the second-order rate constant.

Integration of 17 leads to Equation 18.

$$1/c - 1/c_0 = kt \quad (18)$$

The slope of the plot $1/c$ versus time gives the second-order rate constant. The intercept $1/c_0$ gives initial concentration.

Table 9 and figure 7 show the data for a typical kinetic run on exo-epoxide-endo-ester XXXV.

Although exo-ester-exo-epoxide had been distilled and checked for purity by glc (96 percent was exo-epoxide), trouble was encountered in the kinetic run. The reaction stopped at what was anticipated to be 32 percent. For a period of over five hours there was no decrease in base concentration. It was calculated that the initial ester concentration must have been not 0.0197 M as had been calculated

Table 9. Alkaline Hydrolysis^a of Ester XXXV
in 50 Percent Ethanol at 25°C

time (min)	back titration ml	c base X 10 ²	1/c
10.65	0.990	1.93	51.81
33.30	1.066	1.79	55.86
60.85	1.190	1.54	64.94
83.55	1.252	1.41	70.92
110.15	1.330	1.26	79.36
137.59	1.396	1.13	88.50
184.55	1.488	0.95	105.26

^aTen ml of 1.97×10^{-2} N base containing 0.0386 g
(1.97×10^{-4} mole) with one ml aliquots quenched in one ml
 3.88×10^{-2} HCl and back titration with 1.97×10^{-2} N base.

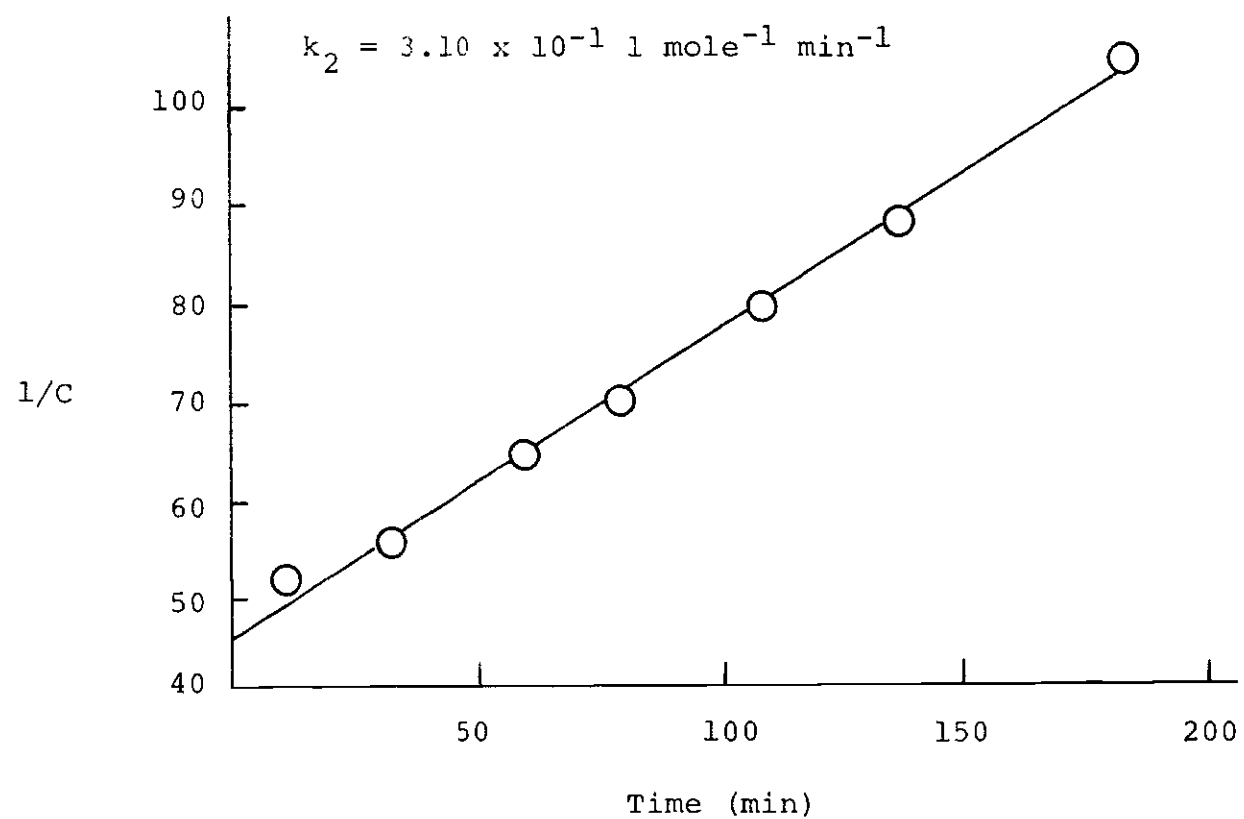


Figure 7. Second-order Kinetic Plot for the Alkaline Hydrolysis of Ester XXXV

from the weight but only 0.0061 M as calculated from base consumption. Further checking of the ester by glc on another column (SE-30, 160°C) revealed the presence of an unknown peak which had not shown up on the tris(cyanoethoxy)-propane column. Since this other compound had not seemed to interfere with the ester hydrolysis and since insufficient epoxide of appropriate exo-endo ratio was available to attempt to remove the offending impurity, the kinetic data gathered was used.

The integrated form for the second-order rate equation, when initial concentrations are unequal, is given by Equation 19 (74),

$$\frac{2.303}{A_0 - B_0} \log \frac{AB_0}{A_0B} = kt \quad , \quad (19)$$

where A_0 and B_0 are the initial concentrations of the reactants and A and B their concentrations at time t . A plot of $\log \frac{AB_0}{A_0B}$ vs t is linear and has a slope = $\frac{A_0 - B_0}{2.303} k$.

Table 10 shows the data for one of these runs and figure 8 shows the kinetic plot. Each of the esters was run from three to six times and their second-order rate constants averaged.

Table 10. Alkaline Hydrolysis of Ester XXXVIII in
50 Percent (Weight) Aqueous Ethanol at 25°C^a

t min	ml OH ⁻ back titrant	conc. base X 10 ²	conc. ester X 10 ²	log $\frac{AB_0}{A_0B}$
0	---	1.93	0.61	0
18.95	1.036	1.88	0.56	0.026
50.20	1.102	1.75	0.43	0.109
90.15	1.138	1.68	0.36	0.170
136.50	1.150	1.66	0.34	0.190
242.15	1.212	1.54	0.22	0.342
571.20	1.328	1.32	0.00	---
866.75	1.326	1.32	0.00	---

^aTen ml of 1.93×10^{-2} N base containing 0.0386 g ester (0.0061 mole by correction) with one ml aliquots quenched in one ml 3.88×10^{-2} N HCl and back titration with 1.93×10^{-2} N base.

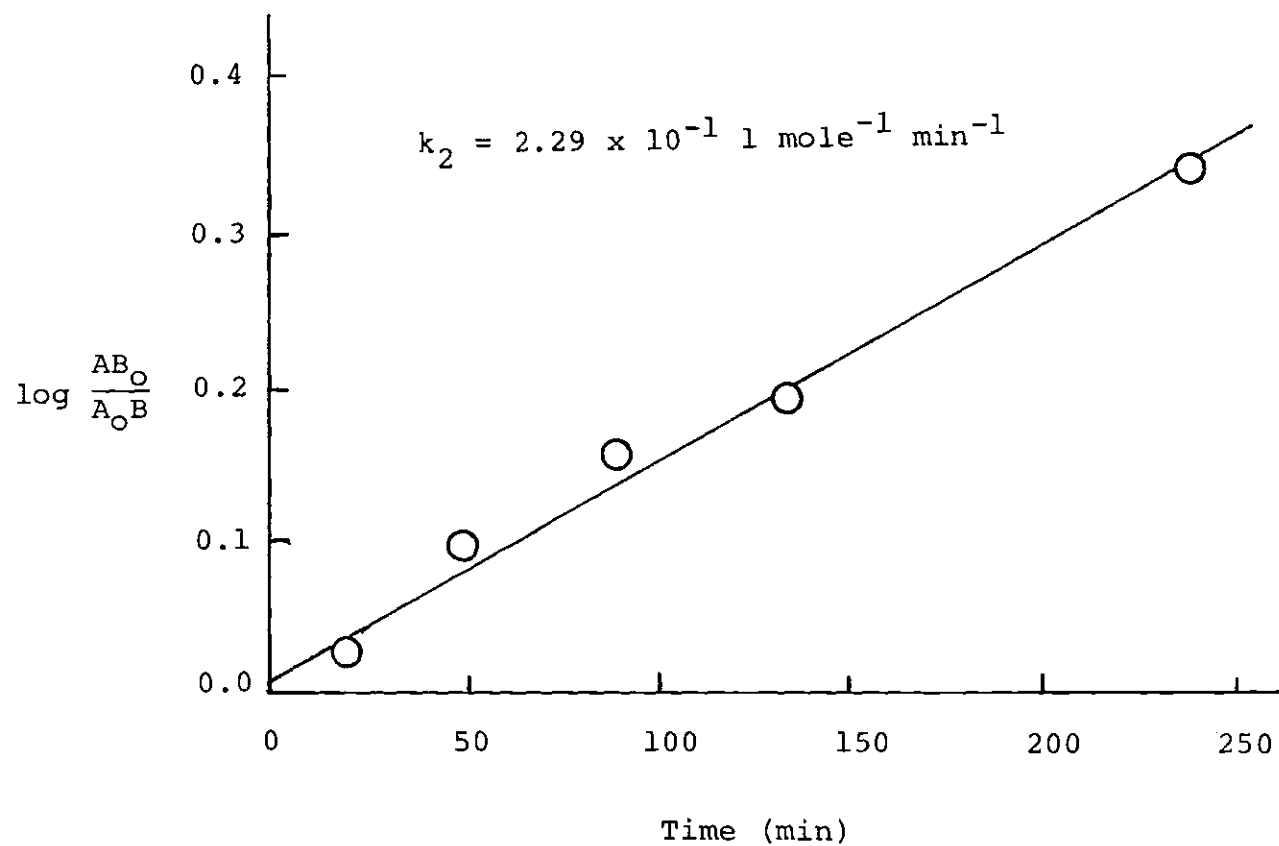


Figure 8. Second-order Kinetic Plot for the Alkaline Hydrolysis of Ester XXXVIII

CHAPTER VII

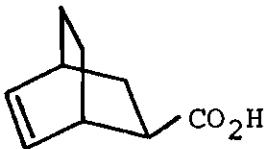
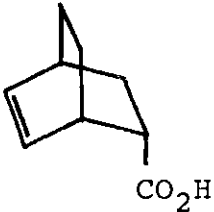
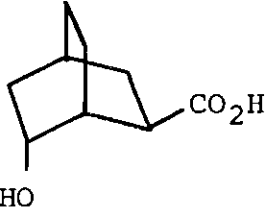
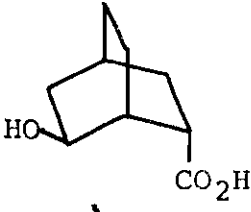
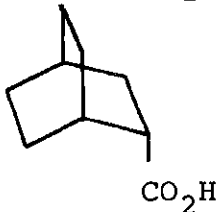
DISCUSSION OF RESULTS - SECTION II

Table 11 summarizes the pKa's of the five bridge substituted acids as measured at 25°C in aqueous ethanol.

If the inductive effect is the only effect operating in the transmission of non-conjugative substituent effects, then clearly acids XXV and XXXIV should have the same dissociation constants since the number of bonds between the substituent and reaction center are the same. The hybridization of the intervening σ framework should also be the same. However we find a difference of 0.21 pKa units in the two acids, indicating some inadequacy in the inductive effect.

To date the strongest evidence for the field effect has been the reversal of normal substituent effects in the 8-substituted-9,10-ethanoanthracene-1-carboxylic acids (25) and 8-substituted-1-naphthoic acids (26). However the reaction center and substituent are so situated that it is easy to envision direct interaction of the solvent spheres of the two centers which might stabilize the unionized form of the acid and cause some of the reversal noted.

Table 11. pKa's of Bridge Substituted
Bicyclo[2.2.2]octanes, 25°C

Compound	pKa
XIX 	6.554 ± 0.005
XX 	6.606 ± 0.005
XXV 	6.470 ± 0.004
XXXIV 	6.261 ± 0.002
XXVIII 	6.722 ± 0.006

This is not to imply that angular dependence was not observed, only that the solvation factor may or may not be important. It is considerably more difficult to envision such an interaction between the hydroxyl and carboxyl group in both XXV and XXXIV.

That there is a dependence of substituent effect on angle and distance is fairly evident. Examination of the nature of this dependence was checked by using equation 2 with Tanford's modification. Table 12 summarizes the parameters and calculated $\log K_X/K_H$ values for the isomeric acids XXV and XXXIV. The calculations of R and θ were made assuming normal bond angles and lengths and an untwisted bicyclooctane nucleus in the absence of specific information to the contrary. X-ray analysis of 1-substituted and 1,4-substituted bicyclooctanes have indicated little or no twist about the 1,4 bond axis (75,76) with normal bond lengths and angles throughout. Whether this is the case with the bridge substituted compound is unknown. However examination of Dreiding models reveals that even for substantial torsional angles the parameters R and θ remain very nearly constant.

The values of $\log K_X/K_H$ predicted are seen to be substantially in agreement with experiment for XXV but over

Table 12. Calculated Values for $\log K_X/K_H$ and Parameters for Isomeric 6-Hydroxybicyclo[2.2.2]octane-2-carboxylic Acids at 25°C

Acid	Parameters		θ°	Tanford Sphere De	$\log K_X/K_H$ calcd.	$\log K_X/K_H$ exp.
	$R, \text{\AA}$	μ, D				
XXV	5.50	2.10	70°32'	4.26	0.21	0.25
XXXIV	4.61	2.10	33°10'	3.80	0.89	0.46

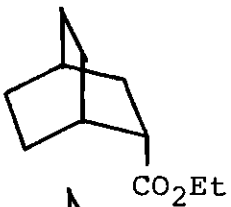
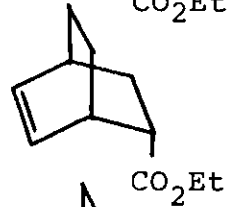
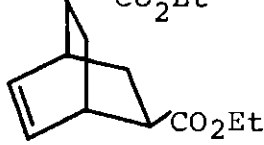
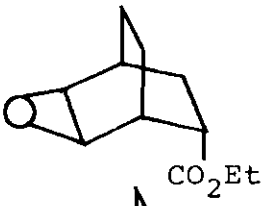
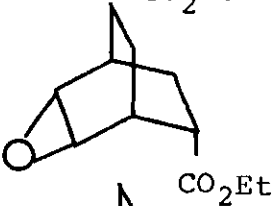
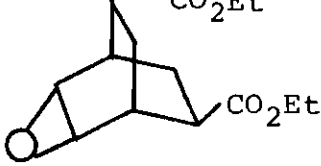
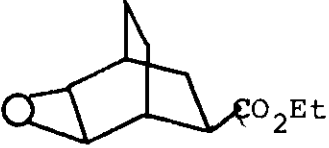
predict the dissociation constant for XXXIV by a factor of two. This may be a result of the fact that the calculation of ΔE by the Tanford method places no importance on the specific location of substituent and reaction center on the hydrocarbon framework, when in fact they may be closer to the surface of the solvent continuum in one case than the other. It is encouraging however that the stronger of the two acids XXXIV is the one predicted by the field effect to be stronger.

Table 13 summarizes the second-order rate constants for the alkaline hydrolysis of the bicyclic esters at 25°C in 50 percent (weight) aqueous ethanol.

Again one notices that the inductive effect would predict the same rates for the hydrolyses of esters XXXV, XXXVI, XXXVII and XXXVIII. With the exception of XXXVI, the epoxide ring and the carboxyl group are in the same steric environment from one ester to the other. The number of bonds from substituent to reaction center is again constant as would be the expected hybridization of the carbon framework. Any direct interaction of the solvent spheres of reaction center and substituent would be difficult to envision except in the case of compound XXXVI.

Examination of the rate constants reveals rather

Table 13. Second-Order Rate Constants for Alkaline Hydrolysis of Bridge Substituted Bicyclo[2.2.2]octane Esters

Compound		$k - 1/\text{mole min} \times 10^2$
XXIX		2.160 ± 0.003
XXVI		4.58 ± 0.03
XXVII		2.75 ± 0.01
XXXV		31.2 ± 0.4
XXXVI		0.442 ± 0.014
XXXVII		5.59 ± 0.06
XXXVIII		21.7 ± 0.9

diverse second-order rate constants for these isomeric compounds in contrast to the behavior predicted by the σ -inductive effect theory. These differences may be examined in terms of the field effect.

It has been proposed that relative rates of reaction of substituted compounds $\log k_X/k_H$ may be determined by equation 20 (7),

$$\log k_X/k_H = \frac{e\mu \cos \theta}{2.3 kTR^2De} \quad (20)$$

which is analogous to equation 2 used to correlate relative acidities. All symbols have their usual meanings.

Table 14 summarizes the parameters, calculated $\log k_X/k_H$, and experimental $\log k_X/k_H$ values for the isomeric epoxy esters. In this case the value of R was taken as the distance from the midpoint of the dipole (the line joining oxygen and the center of the C4-C2 bond) to the carbonyl carbon atom. The microwave spectrum of cis-2,3-epoxybutane has shown the dihedral angle between the epoxide ring and the C₁, C₂, C₃, C₄ plane to be 110° (77). Since the epoxides with which we are concerned are buttressed against the methylene bridge, the dihedral angle between the epoxide ring and the C₁, C₂, C₄, C₅ plane was chosen to be 120°. Sample calculations have shown $\log k_X/k_H$ values to

Table 14. Parameters and Calculated Values of $\log k_X/k_H$ for Alkaline Hydrolysis of Isomeric Epoxy-bicyclo[2.2.2]octane esters at 25°C

Ester	Parameters		θ°	Tanford Sphere De	$\log k_X/k_H$ calcd.	$\log k_X/k_H$ exp.
	$R, \text{\AA}$	μ, D				
XXXV	3.76	2.01	19°52'	3.35	1.60	1.16
XXXVI	2.95	2.01	107°16'	2.88	-0.96	-0.69
XXXVII	4.21	2.01	73°10'	3.54	0.38	0.41
XXXVIII	4.53	2.01	39°54'	3.75	0.82	1.00

be relatively insensitive to small changes of angle since as the distance increases, $\cos \theta$ increases. The value of μ was found to be 2.01 also from the microwave spectrum (77). Again the values of D_e were calculated by the Tanford modification for a spherical cavity.

Examination of Table 14 reveals rather good correlation between the predicted and actual $\log k_X/k_H$ ratios. Predictions are off by less than a factor of three in all cases. Some of the discrepancy may be attributable to the fact that the calculation of D_e fails to take into account the specific location of substituents and reaction center. Examination of structure XXXVIII for example reveals that the lines of force would seem to pass more through the hydrocarbon framework than is the case with XXXV or XXXVII. However the calculated values of D_e are 3.75, 3.35 and 3.54 respectively. It is also possible that the value of μ ought to be smaller since the μ used came from gas phase measurement rather than solution measurement. There is also the possibility that the substituent may induce solvation interactions at the site of the reaction center. This possibility might be eliminated by studying reactions of the different isomers in solvents of the same bulk dielectric but with different solvating power. Compound XXXVI would be expected to show a somewhat depressed rate due to steric effects.

Empirical correlation by the use of σ_I would predict equal values of $\log k_X/k_H$ and $\log K_X/K_H$ of all isomers studied. However it is instructive to note that the Dewar-Grisdale approach to the isomeric epoxides would predict equal values of $\log k_X/k_H$ for compounds XXXV and XXXVI and for compounds XXXVII and XXXVIII since the reaction center is equidistant in each case from the carbons to which the substituent is bound. This approach is obviously inadequate to the present case.

It is satisfying to note that the field effect allows one to predict the proper order for the rates of alkaline hydrolysis. This provides additional evidence for the importance of this effect in the transmission of substituent effects in non-conjugated systems. This is not to say that the σ -inductive effect is not a contributing factor because the two effects may be operating simultaneously.

CHAPTER VIII

CONCLUSIONS - SECTION II

The angle and distances at which substituents are located with respect to a reaction center have been shown to be important determinants in the relative reactivities of isomeric molecules in contrast to the simple predictions of the σ -inductive effect theory. This is taken as evidence for the operation of a field effect.

Correlations between currently accepted versions of the field effect and experiment are excellent in view of the limitations of those theories.

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VITA

William Franklin Fisher, the son of Mr. and Mrs. Franklin R. Fisher, was born April 24, 1943, in Lewisburg, Pennsylvania. From 1943, he resided in Watsontown, Pennsylvania, and attended public schools until his graduation from Warrior Run Area High School in June, 1961. He entered Juniata College in September of 1961 and graduated with a B.S. in chemistry in June, 1965. He entered the graduate school of the Georgia Institute of Technology in September, 1965 and completed requirements for the degree of Doctor of Philosophy in Chemistry in September, 1970. He is a member of the American Chemical Society.

On September 4, 1965 he married the former Verna Faye Laidacker of Turbotville, Pennsylvania. He is the father of two sons, Thomas William and Michael David. He has accepted a position on the faculty of the School of Chemistry at the Georgia Institute of Technology, Atlanta, Georgia.